HPV Update: Incidence, Sequele, Screening, and Prevention

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Disclosures
- Patricia J Sulak MD has been a member of advisory boards and a speaker for Merck Inc
- There will be no off label discussions of FDA approved products in this presentation
- Patricia J Sulak MD served as Chair of the ACOG Gynecology Practice Bulletin in 2002 that approved the American Cancer Society guidelines for Cervical Cancer Screening

HPV
Nonenveloped double-stranded DNA virus
- >100 types identified
- Species specific
- 30–40 infect anogenital area
- High risk / oncogenic types:
  - HPV 16 & 18 acc. for most cervical cancers.
- Low risk /nononcogenic types:
  - HPV 6 & 11 cause most genital warts.

Clinical Spectrum of HPV Infection
- Non-genital
  - Symptomatic
- Genital
  - Asymptomatic
- Benign
  - Regression
- Premalignant
  - Persistence
- Malignant
  - Progression

The majority of HPV infections are asymptomatic, unrecognized, or subclinical, and usually self-limited.

Sexually Transmitted HPV Infection
- Warts, Intraepithelial Neoplasia (dysplasia), or Cancer:
  - anus
  - vagina
  - cervix
  - penis
  - scrotum
  - urethra
  - mouth/throat

Most with HPV will not develop symptoms or sequelae

HPV Types and Cancer Risk
- Low to Negligible Risk:
  - 6,11,40,42,43,44,54,61,70,72,81 (warts, low grade abnor. Pap smears, laryngeal warts)

- High Risk:
  - 16,18,31,33,35,39,45,51,52,56,58,59,68,73,82
    (low grade and high grade abnor. Pap smears, cancers)

Am J Obstet Gynecol 2003; 189:118-20
Transmission of Genital HPV Infection

- Sexual contact: genital-genital, oral-genital, genital-anal
- Perinatal (birth): neonatal laryngeal papillomatosis; HPV 6 or 11
- Other means
  - fomites?
  - digital?

Prevalence of Genital HPV Infection

- est. over 75% of sexually active women have been infected;
- approximately 1 in 4 women (ages 14-59) have evidence of current infection
- 1% have genital warts
  
  JAMA 2007; 297(8): 813-19

Concordance of human papillomavirus in the cervix and urine among inner city adolescents

- screened 80 sexually active adolescents ≤ 20 y.o.a.
- prevalence of HPV: 90% in cervix and 75% in urine
- most common HPV type was HPV 16
- 38% had abnormal Pap smears (all low grade except two)
- other STDs: chlamydia 15%, gonorrhea 6.3%, trichomonas 11.3%


Natural History of Cervicovaginal Papillomavirus Infection in Young Women

- 608 female college students examined/tested for HPV every 6 months for 3 years
- 26% were HPV-positive at initial visit;
- 60% infected with HPV at some time during the three year period including

  Ho et al: NEJM 1998;338:423-8

Natural History of Cervicovaginal Papillomavirus Infection in Young Women

- average duration of HPV infection: 8 months
- 70% cleared infection by 1 year
- 90% cleared infection by 2 years
- risk of dev. cervical dysplasia (abnormal Pap) assoc. with persistent infection with a high risk type for at least 6 months

  Ho et al: NEJM 1998;338:423-8

Incidence of HPV Infection

- One of the most common STDs (est. 6,200,000 new cases annually)
- peak rates in women ≤ 25 years old
- clearance of infection over time in most women and men
- Some (?10%) remain chronically infected

  Perspectives on Sexual and Reprod Health 2004; 36(1): 6 - 10
Sequele of Genital HPV Infection

- Warts
- Intraepithelial Neoplasm (i.e. dysplasia / precancerous)
- Cancer

Genital Warts
Estimated number of new cases per year in the United States:
- 1 million

Estimated number of sexually active adults with clinically visible genital warts:
- 1 in 100

Estimated number of people who will develop genital warts in their lifetime:
- 1 in 10

Genital Warts: Symptoms

- Most asymptomatic
- Itching, burning, bleeding, pain with intercourse
- Obstruction if large mass

US Treatment Guidelines

Patient Applied

- Podofilox
- Imiquimod
- Sinecatechins

Provider Administered

- Cryotherapy
- Podophyllin
- TCA/BCA
- Surgical Removal

HPV and Abnormal Pap Smears

- Est. 55 million Pap smears in U.S. yearly
- 3.0 million with low grade abnormalities annually (atypical cells, low grade)
- 500,000 with high grade abnormalities annually (moderate to severe dysplasia)

National Cancer Institute, March 2007
Penile Lesions and HPV in Male Sexual Partners of Women with CIN

- Screened 175 male sexual partners of women with cervical dysplasia
- Penile lesions were seen in 68% of the male sexual partners with peniscopy
- HPV was detected in 59% of the penile scrapings (many specimens did not have enough cells to evaluate adequately)
- High risk HPV types were found in 94% of those that tested positive for HPV


Screening for Cervical Cancer

Pap Smear

ACOG Cervical Cytology (Pap Smear) Guidelines 2009

- First pap smear at age 21, regardless of sexual hx
- Ages 21-29: every 2 years
- Over 30: every 3 years
  - Can also do high-risk HPV DNA testing
  - When to stop???? Age 65?, 70? Assess risk
- If h/o TX for CIN 2/3, annual testing x 20yrs
- Pap not necessary if hysterectomy for benign disease

Rationale for No Paps Under Age 21

- Cervical dysplasia is common but most lesions spontaneously resolve
- Cervical cancer is very rare under age 21 (0.1% of all cases)
- 1 – 2 cases per 1,000,000 females aged 15 – 19 (average 14 cases / year in this age group)
- Significant increase in premature births in women treated for cervical dysplasia


Cervical Cancer in U.S.
Estimates for 2010

- 12,200 cases - invasive cervical cancer
- 4,210 deaths from cervical cancer
- 1 out of 50 cancer-related deaths
- 0.4% of all female deaths

American Cancer Society - Facts and Figures 2010

Sexually Transmitted Infection as A Cause of Anal Cancer

Case-control study comparing epid. anal cancer to normal controls and adenocarcinoma of the rectum

- 1st intercourse at ≤16 years of age at increased risk compared to those >20 years of age at 1st intercourse

- Risk factors also included male homosexual contact, genital warts, and receptive anal intercourse in women

- High risk types of HPV, esp HPV-16, were detected in 84% of anal-cancer specimens

### Anal Cancer
- ACS estimates 2010: 5,260 cases / 720 deaths
- Incidence has increased over past 30 years
- High risk: MSM and immuno-compromised
- Women with a history of cervical or vulvar cancer / carcinoma-in situ have a 14-fold increased risk of anal cancer

*Obstet Gynecol* 2011; 117: 643-9

### Genital HPV Types Associated with Oropharyngeal Disease
- HPV in the genital area can be transmitted to the oral cavity (similar to HSV 1 and 2 transmitted through oral / genital contact)
- The mouth and throat are lined with squamous epithelium, the type lining HPV can infect
- Recent studies are now implicating HPV in benign (warts) and malignant lesions of the mouth and throat

### Laryngeal Papillomatosis
**Description of clinical entity:**
- Benign growths of respiratory tract in juveniles and adults
- Caused by HPV 6 and HPV 11
- Usually acquired during birth
- Many patients require multiple surgeries, 1-3% die of disease

### Case-Control Study of HPV & Oropharyngeal Cancer
- 100 patients with newly diagnosed oropharyngeal cancer & 200 control patients without cancer; to evaluate associations with HPV infection
- Lifetime number of vaginal sex partners & oral sex partners was associated with an increase risk of oropharyngeal cancer
- Oropharyngeal cancer was statistically associated with HPV type 16 [OR 14.6 (CI 6.3 – 36.6)], regardless of alcohol and tobacco use


### HPV and Oropharyngeal Cancer
**NEJM 2010; 363: 24-35**
- 323 patients with Stage III or IV oropharyngeal squamous cell CA tested for HPV DNA
- 63.8% (206 of 323) were HPV + of which 96% (198 of 206) were HPV-16
- Of 206 HPV+: 86% male / 14% female
- HPV + were younger (median age 53.5) compared to HPV – (median age 57)

### HPV and Oropharyngeal Cancer
**NEJM 2010; 363: 24-35**
- HPV+ patients had better 3 year survival (82.4% vs 57.1%)
- Risk of death and cancer relapse increased for each pack-year of tobacco smoking
- HPV status was the major determinant of overall survival, followed by # pack-years smoking, and then nodal status
- HPV+ and HPV – oropharyngeal SCCa are distinct with different causes, risk-factor profiles, and survival outcomes
The Burden of Disease Caused by HPV: Beyond the Numbers

Financial
Emotional
Physical


Anxiety
Fear of cancer
Financial burden
Lost productivity
Pain
Stigma
Symptoms
Negative self-perception
Sexual difficulties
Depression
Social isolation

Reducing the Risk of HPV Transmission

- Abstinence from genital contact
- Lifetime mutual monogamy
- If used correctly, condoms can help reduce the risk of HPV infection. However, the level of protection from HPV infection with condom use has not yet been determined.

Risk of Cervical Lesions and Cancer in Women Exposed to HPV at a Young Age

Relative risks for CIN and invasive cancer increase with decreasing age of first sexual intercourse.

Age at First Intercourse (Years)
- ≥ 23 or Never
- 18–22
- ≤ 17

Cervical Dysplasia/Cervical Cancer

“The high risk woman, it is generally recognized, is an individual who becomes sexually active in the mid-adolescent years and has a tendency to have multiple sexual partners.”

Adolescent Cervix:
Columnar → Metaplastic → Squamous

Disaia and Creasman, Clinical Gynecologic Oncology, 2007

HPV Vaccines

Current prophylactic vaccines:
- Recombinant L1 HPV capsid proteins that form “viral like” particles (VLP)
- Non-infectious and non-oncogenic
- Produce high levels of neutralizing antibody
- Not expected to cause regression of established lesions

Disease Burden From HPV Types 6, 11, 16, and 18

<table>
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<tr>
<th>HPV Type</th>
<th>Approximate Disease Burden</th>
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<tr>
<td>16 and 18</td>
<td>≥70% of cervical cancer and moderate/severe dysplasia of cervix, vagina, and vulva</td>
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<tr>
<td>6, 11, 16, and 18</td>
<td>≥35%–50% of all mild dysplasia of cervix, vagina, and vulva</td>
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<tr>
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<td>≥99% of genital warts cases</td>
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AIS = adenocarcinoma in situ; CIN = cervical intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia.
**HPV Vaccines**

- **Gardasil®**
  - Approved for prevention of genital warts & precancer/cancer of the cervix, vulva, vagina in females, anal cancer in males & females, and genital warts in males
  - Induces antibodies for HPV 6,11,16, & 18
  - Approved for use in males and females 9 – 26 years for age
  - 3 injections: 0, 2 months, and 6 months

**ACIP Recommendations**

- Routine vaccination of females aged 11 or 12 with 3 doses, can be started at age of 9
- Also recommended for females aged 13 – 26 who have not been previously vaccinated or who have not completed the full series.
- May be given to males aged 9 – 26 to reduce likelihood of acquiring genital warts or anal cancer.

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**Costs of HPV Infection**

- estimates range from $1.6 billion to $6 billion
- 2nd most costly STD after HIV infection
- intangible costs: emotional pain, anxiety, disrupted relationships
- HPV-related mortality is slightly lower than that of HIV for women in U.S.

CDC, Dec 1999

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**ACIP* Recommendations for HPV Vaccines**

**Cervarix®**

- Approved for prevention of cervical cancer and precancers
- Induces antibodies for HPV 16 & 18
- Approved for use in females 10 – 25 years of age
- 3 injections: 0, 1 month, and 6 months

**ACIP Recommendations**

- Routine vaccination of females aged 11 or 12 with 3 doses, can be started at age of 10
- Also recommended for females aged 13 – 25 who have not been previously vaccinated or who have not completed the full series.

*Ideally, vaccine should be administered before potential exposure to HPV through sexual contact.*

*Advisory Council on Immunization Practices