Genital Human Papillomavirus

Patti E. Gravitt, PhD
Johns Hopkins University
Section A

Biology of HPV
HPV is a double stranded, closed circular (episomal) DNA virus with a genome size of 8,000 base pairs.

Notes: * URR = upstream regulatory region
HPV Genotypes

- More than 100 genotypes identified which infect human epithelium, ~50 which specifically infect the anogenital tract
- Approximately 17-18 are high risk, or oncogenic
  - HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82
  - HR HPV infection is necessary, but not sufficient for development of invasive cervical cancer
- Remaining HPV types are not associated with cancer risk (low risk or non-oncogenic), but they can cause low grade cervical abnormalities or benign proliferative warts (especially HPV 6 and 11)
Over 50% of invasive cervical cancers are attributable to HPV 16

Approximately 70% are attributable to HPV 16 or 18

Source: Bosch, et al. (1995), *JNCI*
HPV Life Cycle

HPV infects basal epithelium at sites of micro-trauma

Capsid gene expression and infectious particle released in exfoliating squamous cells

Viral genome amplification in suprabasal epithelial cells
HPV Life Cycle

Lack of epithelial differentiation, cellular genome instability, sometimes viral DNA integration

Invasion through the basement membrane

Notes on source material are available by clicking the Notes tab.
Section B

Epidemiology and the Natural History of HPV Infection
Working Model of Cervical Carcinogenesis: Risk Factors of Infection

- Sexual behavior
- Partner’s sex history

Normal cervix \(\rightarrow\) HPV infection \(\rightarrow\) Persistence \(\rightarrow\) High grade neoplasia \(\rightarrow\) Invasion
Mechanisms of HPV Transmission and Acquisition

- Sexual contact
  - Predominately via penetrative sexual intercourse, including anal intercourse
  - Also genital-genital, manual-genital, and oral-genital non-penetrative contact
    - Can explain some HPV-positive “virgins”
  - Condoms offer modest protection if used correctly and consistently with every sexual contact.
    - Models estimate high per-sex-act transmission probability (40%)
94 students age 18-20 were followed from the time of first sexual intercourse for cervical HPV detection at four month intervals. Cumulative incidence was 20% at six months, 30% at one year, and greater than 50% after four years.

Most HPV Infections Are Transient

- Among young high-risk adolescent/young adult women, 50% of HPV infections clear within eight to twelve months and only ~10% persist past two-and-a-half years.
- Among HIV+, average duration of infection is nearly two years, and more than 25% remain HPV+ after four-and-a-half years of follow-up.

The majority of infections are self-limiting and asymptomatic (~80% of initial HPV infections remain asymptomatic after five years).

HPV infection does not require cell death to complete infectious cycle and therefore causes no local inflammation or ulceration.

Clinical manifestations of infection are screen-detected epithelial abnormalities.
In a study of women 13-22 years of age, there was a 91% probability of regression of LSIL cases within three years. The probability of progression to high grade lesions (HSIL) within the same time frame was 3%.
Current screening targets the identification of high grade lesions at greatest risk of cancer progression (cervical intraepithelial neoplasia grades 2-3, CIN 2/3)

Risk of CIN 2/3 after first HPV infection is significantly higher for HPV 16/18 relative to other high risk genotypes
Younger Women Significantly More Likely to Regress HSIL over Short Follow-Up

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Persistent Lesion</th>
<th>Resolved Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22</td>
<td>4 (11)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>23-27</td>
<td>15 (43)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>&gt;27</td>
<td>16 (46)</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

- In a study of 47 women with HPV, 16 positive CIN 2/3 lesions, 56% of women younger than 22 vs. 6% of women older than 27 resolved their lesions after about four months of follow-up
Epidemiologic Determinants of HPV Persistence, Progression, and Invasion

Fig. 6. Overview of factors most consistently reported to play a role at different stages in the natural history of HPV and cervical neoplasia.

Source: Moscicki AB, Updating the natural history of HPV and anogenital cancer. Vaccine 2006;24 Suppl 3 S42–51. © 2006 Elsevier Ltd. All rights reserved.
Section C

Diagnostics/Treatment
Diagnostics

- HPV is a screen-detected infection
  - Not a reportable STI, population-based surveillance data unavailable
    - New Mexico legislation
- Formerly only identified indirectly by cytologic evidence of infection/neoplasia from Pap smears
- Molecular tests currently available to detect and genotype HPV DNA
Digene Hybrid Capture 2 (hc2)

- Only FDA-approved HPV detection assay
- Targets HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
- Positive result = positive for one or more of the 13 high risk types
  - Some low risk cross-reactivity
HPV Genotyping by Roche Linear Array Assay

- PCR-based test that targets a conserved region of the capsid genome (L1), differentiates presence of 37 high and low risk HPV genotypes
- Allows detection of multiple genotype infections
- Currently research use only (RLU)
Cervical Cancer Screening Guidelines

Age to Begin Screening

- American Cancer Society (ACS) and American College of Obstetrics and Gynecology (ACOG) recommend that you begin screening approximately three years after 1st vaginal intercourse but no later than age 21
- The Pap test should NOT be the basis for onset of gynecologic care
- Adolescents who do not need a Pap should still get appropriate contraceptives services, STD screening, and other preventative health care
Cervical Cancer Screening Guidelines

Screening Frequency/Cessation

- Screening should be done every year with the regular Pap test or every two years using the newer liquid-based Pap test.
- Beginning at age 30, women who have had three normal Pap test results in a row may get screened every two to three years.
  - Another reasonable option for women over 30 is to get screened every three years (but not more frequently) with either the conventional or liquid-based Pap test, plus the HPV DNA test.
- Women 70 years of age or older who have had three or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer screening.
- Women who have had a total hysterectomy (removal of the uterus and cervix) may also choose to stop having cervical cancer screening, unless the surgery was done as a treatment for cervical cancer or pre-cancer.
Indications for HPV Testing

1° Screening in Women over 30

- Concurrent testing
  - Screen with HPV and Pap
  - If either test is positive, follow normal triage strategy and continue with annual screens
  - If both tests are negative, extend screening interval to once every three years

- Sequential testing
  - Screen with HPV test (triage with Pap)
  - Immediate colpo for HPV/Pap positive
  - Retest HPV+/Pap- at one year
Data Supporting Safe Expansion of Screening Interval Following HR-HPV Negative Test

Kaiser Portland NCI Study 1990-1999:

Years of Follow-Up

CIN 2/3

HPV +

HPV -

Section D

Current Trends in the Epidemiology of HPV and Methodological Issues in Research
Normal cervix → HPV infection → Persistence → High grade neoplasia → Invasion

Average Duration 8-12 Months

- Sexual behavior
- Partner’s sex history
- Immune suppression (HIV; Renal transplant)
  - HLA
  - Oc use?
- Viral type
  - Parity
  - Smoking
  - Oc use
  - Inflammation
  - Viral load?
- Angiogenesis
- Adhesion?

Source: Patti Gravitt, PhD. Johns Hopkins Bloomberg School of Public Health
Working Model of Cervical Carcinogenesis

- Normal cervix
- HPV infection
- Persistence
- High grade neoplasia
- Invasion

Average Duration 8-12 Months

- Transmission risk
- Vaccine efficacy
- Sexual behavior
- Partner studies
- Partner’s sex
- History
- Smoking
- Parity
- HLA
- Use?

- Persistence vs. latency
- Natural history in older women
- Type
- Invasion (transplant)
- Mechanism
- Biomarkers
- Cofactors
- Inflammation
- Viral load
- Angiogenesis
- Adhesion

Source: Patti Gravitt, PhD. Johns Hopkins Bloomberg School of Public Health
Sampling

- Not systemic infection (localized to multiple foci of epithelium)
- Each infection may represent independent probability of disease progression vs. infection clearance
Sampling

- Swabs are sampling multiple foci of infections and potentially multiple “independent” lesions
- Biopsies are directed to sites of acetowhite changes indicative of a single lesion
  - Therefore, detection of HPV from biopsy-extracted DNA can help to assign a genotype-specific risk
- Other potential biases in interpretation due to sampling
  - Assuming viral clearance when exfoliated cell sample is HPV negative
  - Estimating viral load when using cumulative viral burden assay (e.g., commercially available hc2)
Less than 50% of specimens that showed multiple HPV types on exfoliated swab resolved to single infection via directed biopsy sampling.
Sampling

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HPV Persistence

- Natural history studies are consistent in observations that normal time-to-clearance is eight to twelve months on average.
- Therefore persistence should be defined as repeated HPV detection for at least twelve months.
- HPV infection is COMMON and heterogeneous.
  - MUST define persistence type-specifically.
Influence of Interval Sampling

Section E

Primary Prevention Opportunities: Prophylactic HPV VLP Vaccines
Virus-Like Particle (VLP) Vaccines

- HPV L1 expressed from a strong heterologous promoter will self-assemble into empty viral particles in yeast, insect, and bacterial cells
- Morphologically indistinguishable from native HPV virions
- Contains no DNA, therefore non-infectious (low risk)
  - Clinical trials demonstrate excellent safety data
- Parenteral vaccination (three doses over seven months) induces nearly 100% protection
## General Population Impact: GARDASIL® Reduced HPV 16- and 18-Related CIN 2/3 or AIS

<table>
<thead>
<tr>
<th>HPV 16- or 18-related CIN 2/3 or AIS</th>
<th>N</th>
<th>GARDASIL or HPV 16 L1 VLP Cases</th>
<th>N</th>
<th>Placebo Cases</th>
<th>% Reduction</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Prophylactic Efficacy*</td>
<td>9,342</td>
<td>1</td>
<td>9,400</td>
<td>81</td>
<td>98.8%</td>
<td>93–100</td>
</tr>
<tr>
<td>HPV 16 and/or HPV 18 Positive at Day One</td>
<td>--</td>
<td>121</td>
<td>--</td>
<td>120</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>General Population Impact†</td>
<td>9,831</td>
<td>122</td>
<td>9,896</td>
<td>201</td>
<td>39.0%</td>
<td>23–52</td>
</tr>
</tbody>
</table>

* Includes all subjects who received at least one vaccination and who were naïve (PCR (-) and sero (-)) to HPV 6, 11, 16, and/or 18 at day one. Case counting started at one month postdose one.
† Includes all subjects who received at least one vaccination (regardless of baseline HPV status at day one). Case counting started at one month postdose one.

Note: Table does not include disease due to nonvaccine HPV types.
Routine HPV vaccination is recommended for females aged 11-12 years. Females as young as nine-years-old may receive HPV vaccination. HPV vaccination is also recommended for females aged 13-18 years to catch up missed vaccine or complete the vaccination series.
There are currently insufficient data to recommend for or against universal vaccination of females aged 19-26 years in the general population.

A decision about whether a woman aged 19-26 should receive the vaccine should be based on an informed discussion between the woman and her health care provider regarding her risk of previous HPV exposure and potential benefit from vaccination.

Ideally the vaccine should be administered prior to potential exposure to genital HPV through sexual intercourse because the potential benefit is likely to diminish with increasing number of lifetime sexual partners.
ACS Guidelines

- HPV vaccination is not currently recommended for women or men over 26 years-of-age
- Screening for cervical intraepithelial neoplasia and cancer should continue in both vaccinated and unvaccinated women according to current ACS early detection guidelines
Screening Changes in Developed World: U.S. Example

- Current screening programs reduce cervical cancer burden by 80%
  - At an annual expense of $4-6 billion
- Addition of vaccine will add substantially to cervical cancer prevention costs
  - Requires revised screening strategies with central role for HPV testing
    - Allow safe expansion of screening interval
    - Sequential screening with HPV test first, followed by Pap
    - HPV genotyping