HPV Epidemiology and Natural History

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Human Papillomavirus (HPV)

- DNA virus
- Infect different areas of skin
- Do not circulate in blood
- Over 100 HPV types
- ≥40 genital HPV types
# Genital/Mucosal HPV Types

<table>
<thead>
<tr>
<th>HPV TYPE</th>
<th>CLINICAL FINDINGS</th>
<th>CANCER POTENTIAL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6, 11</td>
<td>genital warts, low grade lesions, recurrent respiratory papillomatosis (RRP)</td>
<td>Low (negligible)</td>
</tr>
<tr>
<td>40, 42, 54, 55/44, 61, 70, 72, 81, CP6108</td>
<td>low grade lesions</td>
<td>Low (negligible)</td>
</tr>
<tr>
<td>16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82/IS39</td>
<td>low grade lesions, high grade lesions, cancer</td>
<td>High</td>
</tr>
</tbody>
</table>

Uncertain cancer potential: HPV 57, 62, 64/34, 67, 69, 71, 83, 84

* Cancer potential: Muñoz et al., Vaccine 2006;24S3:S3/1
Epidemiology of HPV

• The most common STD worldwide
• Almost all sexually active persons will acquire HPV
• 14.1 million infections new infections per year in the U.S.\(^1\)

Epidemiology of HPV

• Peak prevalence during adolescence and young adulthood

• In sexually active 15-24 year olds, ~9.2 million are currently infected.\(^1\)
  
  – An estimated 74% of new infections occur in this age group.\(^1\)

• Prevalence declines with age

Prevalence of low-risk and high-risk HPV among 4150 14-59 year old females, NHANES 2003-2006

J Infect Dis. 2011;204:566-573

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Modes of HPV Transmission

• SKIN contact, not blood or bodily fluids
• Sexual
  – Intercourse (vaginal or anal) – (most common route)
  – Genital (non-penetrative), oral, digital contact

• Non-sexual
  – Mother to newborn (vertical transmission - rare)
Female Risk of Acquiring Genital HPV Infection from her First Male Sex Partner


*From date of first reported vaginal intercourse with a male partner (Women were censored at reported date of a second sex partner)*
Risk Factors for HPV Infection in Women

• Recent new partners
  – Increased risk with new partners reported in the past year

• Time having known a partner before sex
  – Women knowing their partners for <8 month at greater risk than women knowing their partners for ≥8 months

• Sex partner’s number of previous partners
  – Increased risk with one or more previous partners
  – Even greater risk if the number of previous partners was unknown!

• Inconsistent condom use with new partners
Incidence of Genital HPV Infection by Anatomic Site Among Sexually Active Male University Students (18-23 Years Old)

(Partridge et al. *JID*, 2007;196:1128-36)
Circumcision and HPV?

• A meta-analysis of 21 studies (including 2 RCTs in Africa) showed that HPV was less prevalent in circumcised than uncircumcised men (OR=0.6, 95% CI: 0.4-0.8)\(^1\)
  – No effect on HPV acquisition or clearance

• A longitudinal in young heterosexual men showed no effect on overall HPV acquisition, but multi-focal genital infection was more common in uncircumcised men.\(^2\)

• Does it affect men’s susceptibility to infection and/or infectivity and persistence?

\(^1\)Albero et al, Sex Transm Dis 2012; 39:104-113
\(^2\)Vanbuskirk et al, Sex Transm Dis 2011; 38:1074-81
Duration of HPV Infections

• Vast majority of infections resolve spontaneously (90% within 2 years)
• Duration of infections seems to be shorter in men than in women
• Can’t be sure whether an infection has “cleared” or become “latent”
Duration of HPV Infections

• In newly sexually active female university students, 90% of new infections cleared within 2 years (half cleared within 9.4 months).¹
  – 19% of “cleared” infections were re-detected within 1 year.

Does Re-infection Occur?

- Neutralizing antibodies likely protect against re-infection with the same HPV type.
- Difficult to distinguish re-infection from re-activation.
- Limited epidemiologic data for and against.
Natural History of Cervical Neoplasia: Median Age of Events

- Menarche
- Sexual debut
- HPV infection
- CIN
- **ASC-US** (atypical squamous cells of undetermined significance)
- Incident CIN3/CIS
- Micro invasive CxCa
- Prevalent CIS
- Clinical ICC
Cervical Transformation Zone
(From Schiffman et.al., *Lancet* 2007)

- squamo-columnar junction site
- stratified squamous epithelium
- columnar epithelium
Clinical Findings with Cervical HPV Infection

HPV infects basal cells that will undergo mitosis

Squamous cervical epithelium

Basal cell at junction

Basal membrane

<table>
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<tr>
<th>Normal</th>
<th>CIN1/LSIL (condyloma, productive HPV infection)</th>
<th>CIN2/HSIL (precancer/ productive infection)</th>
<th>CIN3/CIS/HSIL (precancer)</th>
<th>Invasive Cancer</th>
</tr>
</thead>
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Clinical Findings with Cervical HPV Infection

1. Normal
2. CIN1/LSIL (condyloma, productive HPV infection)
3. CIN2/HSIL (precancer/ productive infection)
4. CIN3/CIS/HSIL (precancer)
5. Invasive Cancer
Incidence of HPV-related lesions among 600 female university students
(Winer *JID* 2005;191:731)

<table>
<thead>
<tr>
<th>Among women with:</th>
<th>3-year Incidence</th>
<th>Median Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>incident HPV Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cervical SIL</td>
<td>47%</td>
<td>4 mo.</td>
</tr>
<tr>
<td>CIN2-3</td>
<td>11%</td>
<td>14 mo.</td>
</tr>
<tr>
<td>incident HPV 6 or 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>genital warts</td>
<td>64%</td>
<td>3 mo.</td>
</tr>
</tbody>
</table>
Development of CIN 2,3 in Seattle Study

HPV 16 or 18
Other HPV types

Percentage of Women

Length of Follow-up (months)

0% 10% 20% 30%

0 12 24 36 48

27%

10%

Winer et al. (2005) J Inf Diseases
Duration of HPV-related lesions

- The median duration of low-grade SIL was 5.5 months.

- With treatment, the median duration of genital warts was 5.9 months.

Winer et al (JID) 2005
Risk Factors for Progression to \( \geq \text{CIN 3} \)

- HPV type 16
- Smoking
- HIV
- Hormonal contraceptive use
- Multiparity
Geographic distribution of the world ASIR of cervical cancer, by country, estimated for 2008


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Global Perspective on Cervical Cancer

- 5\textsuperscript{th} most common cancer in humans
- 3\textsuperscript{rd} most common cancer in women
- Relatively early age of death
  - Median of 57 yrs versus 72 yrs for all cancers
Relative Contribution of HPV Types to the Global Burden of Cervical Cancer

Muñoz IJC 2004
Age-Standardized Rates of New Cases of Cervical Cancer per 100,000 Women, 2002

Role of HPV in Cancers

Trottier H et al, Public Health Genomics 2009
Oral HPV

- HPV linked to oropharyngeal squamous cell carcinomas (OSCCs) (~90% due to HPV16)\(^1\)
- Prevalence of oral HPV 16 in U.S. is 1%.\(^2\)
  - Oral HPV 3x more common in men than in women.
  - Bimodal age distribution (peak prevalence in adults aged 30-34 and 60-64 years)
- Incidence of OSCCs is increasing, particularly in men.\(^3\)

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\(^2\) Gillison et al. JAMA 2012; 15(307):693-703  
\(^3\) Chaturvedi et al. J Clin Oncol 2011;29(32):4294-301
Number of new HPV-associated cancers overall, and by sex, in the United States, 2009


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Annual Global Burden of HPV-Related Cancers

• 530,000 cervical cancers (270,000 deaths)
  – 88% in developing countries

• 97,200 non-cervical cancers (51,000 in men and 46,000 in women), including penile, vaginal, vulvar, anal, oropharyngeal