Nuns, Warts, Viruses, and Cancer

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Human papillomavirus

- Small DNA tumörvírus
- Species specific
- Epitheliotropic
- >100 HPV types
- Some HPV types are cancer associated
- Ffa cervixcancer/lívmoderhalscancer
Human papillomavirus (HPV)

Cutaneous

Mucosal

Low-risk HPV

High-risk HPV
Cutaneous HPVs may cause skin warts
Human papillomavirus (HPV)

- Cutaneous
- Mucosal
  - Low-risk HPV
  - High-risk HPV
High-risk types have been associated with cancer. (HPV-16 and -18 (>70%))

Low-risk types are not cancer-associated. (HPV-6)
HPV typer
Papillomavirus Episteme
A resource of the Bioinformatics and Computational Biosciences Branch at the NIAID Office of Cyber Infrastructure and Computational Biology
HPV and *Homo sapiens* have co-evolved.
Identification of HPV infection in mummy of Mary of Aragon (1568)
HPV – the most common sexually transmitted infection in the world.

- >50% of the sexually active population have had an HPV infection.

- 8% of the entire human population have an ongoing mucosal HPV infection.
Papillomavirus infection is common in young women

Prevalence rates of HPV infection (%)

Age

Age-specific HPV prevalence in regions among women with normal cytology

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Africa</th>
<th>South and Central America</th>
<th>Europe</th>
<th>North America</th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
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<td>25–34</td>
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<td>35–44</td>
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<td>45–54</td>
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<td>&gt; 54</td>
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</table>
HPV-infections are normally cleared within 12-24 months.

High-risk HPV types may persist.

Persistent HPV infections can progress to cancer.
HPV infection of uterine cervix
HPV infections can cause lesions in the genital epithelium

- HPV infection may cause lesions in the cervical epithelium.
- May be low- or high grade.
- “Cervical intraepithelial neoplasias (CIN)” can be graded as CIN1-CIN3.
- CIN3=cancer in situ.
Cervical epithelium
Normal cervical epithelium

High grade cervical lesion

(hnRNP A1 and SR proteins)
HPV associated lesions in cervical epithelium.

NORMAL  LSIL  HSIL  TUMOR

(hnRNP A2/B2)
Natural course of HPV infection

In 1 year
- HPV Infection
- CIN 1
- Cleared HPV infection

In 5 years
- Persistence
- CIN 2/3

15-20 years
- Cervical cancer
Natural course of HPV infection

<table>
<thead>
<tr>
<th>CIN</th>
<th>Regress</th>
<th>Progress to cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>60%</td>
<td>1%</td>
</tr>
<tr>
<td>II</td>
<td>40%</td>
<td>5%</td>
</tr>
<tr>
<td>III</td>
<td>33%</td>
<td>&gt;12%</td>
</tr>
</tbody>
</table>

Cervical cancer is a very rare outcome of a very common infection
Cervical cancer

- Mean age 51yrs (but 2 peaks).
- 530,000 diagnosed cases/yr
- 275,000 deaths/yr
# Cancer cases in Sweden 2009.

<table>
<thead>
<tr>
<th>Cancerform</th>
<th>% av alla cancerformer</th>
<th>Antal fall/år</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bröstcancer</td>
<td>29,2</td>
<td>7049</td>
</tr>
<tr>
<td>Tjocktarmscancer</td>
<td>8,4</td>
<td>2034</td>
</tr>
<tr>
<td>Skivepitelcancer i huden samt övrig hudcancer</td>
<td>7,4</td>
<td>1798</td>
</tr>
<tr>
<td>Lungcancer</td>
<td>6,5</td>
<td>1576</td>
</tr>
<tr>
<td>Livmoderkroppscancer</td>
<td>5,7</td>
<td>1369</td>
</tr>
<tr>
<td>Malignt melanom i huden</td>
<td>4,9</td>
<td>1182</td>
</tr>
<tr>
<td>Maligna lymfom</td>
<td>3,7</td>
<td>884</td>
</tr>
<tr>
<td>Ändtarmscancer</td>
<td>3,5</td>
<td>850</td>
</tr>
<tr>
<td>Äggstockscancer</td>
<td>3,0</td>
<td>724</td>
</tr>
<tr>
<td>Hjärntumörer och cancer i övriga nervsystemet</td>
<td>2,8</td>
<td>666</td>
</tr>
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<td>...</td>
</tr>
<tr>
<td>Livmoderhalscancer</td>
<td>1,9</td>
<td>450</td>
</tr>
</tbody>
</table>
# Deaths due to cancer, Sweden 2009.

<table>
<thead>
<tr>
<th>Cancerform</th>
<th>Totalt antal döda/år</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungcancer</td>
<td>3479</td>
</tr>
<tr>
<td><strong>Prostatacancer</strong></td>
<td>2 473 (endast män)</td>
</tr>
<tr>
<td><strong>Bröścieancer</strong></td>
<td>1 515 (i princip endast kvinnor) (nio är män)</td>
</tr>
<tr>
<td>Tjocktarmscancer</td>
<td>1 790</td>
</tr>
<tr>
<td>Julspettkörtelcancer</td>
<td>1 586</td>
</tr>
<tr>
<td>Maligna lymfom</td>
<td>920</td>
</tr>
<tr>
<td>Ändlarmscancer</td>
<td>823</td>
</tr>
<tr>
<td>Magsäckscancer</td>
<td>738</td>
</tr>
<tr>
<td>Urinbläsa/urinvägar</td>
<td>701</td>
</tr>
<tr>
<td>Hjärntumor och nervsystem</td>
<td>646</td>
</tr>
<tr>
<td>Levercancer</td>
<td>634</td>
</tr>
<tr>
<td><strong>Äggstockcancer</strong></td>
<td>620 (endast kvinnor)</td>
</tr>
<tr>
<td>Njurcancer</td>
<td>580</td>
</tr>
<tr>
<td>gallbläsa</td>
<td>514</td>
</tr>
<tr>
<td>Multipelt myelom</td>
<td>478</td>
</tr>
<tr>
<td>Malignt melanom</td>
<td>443</td>
</tr>
<tr>
<td>Leukemi</td>
<td>411</td>
</tr>
<tr>
<td>Matstrupscancer</td>
<td>386</td>
</tr>
<tr>
<td>Läpp, munhåle och svalg</td>
<td>255</td>
</tr>
<tr>
<td>Mjukdels- och skelettcancer</td>
<td>181</td>
</tr>
<tr>
<td><strong>Livmoderkroppscancer</strong></td>
<td>148 (endast kvinnor)</td>
</tr>
<tr>
<td><strong>Livmoderhalscancer</strong></td>
<td>125 (endast kvinnor)</td>
</tr>
<tr>
<td>Sköldkörtelcancer</td>
<td>66</td>
</tr>
<tr>
<td>Hudcancer</td>
<td>64</td>
</tr>
<tr>
<td>Struphuvudcancer</td>
<td>56</td>
</tr>
<tr>
<td><strong>Barnancer</strong> (barn under 15 år)</td>
<td>46</td>
</tr>
<tr>
<td>Tumörer i endokrina körtlar (exklusive sköldkörteln)</td>
<td>25</td>
</tr>
<tr>
<td><strong>Testiklancer</strong></td>
<td>16 (endast män)</td>
</tr>
</tbody>
</table>

*Socialstyrelsen*
Incidence rate of cervical cancer

Figure 5  Cervical cancer, global map showing estimated age-standardized (world standard) incidence rate per 100,000 in 2008 (all ages). Based on GLOBOCAN 2008 <cross-ref refid="bib0065">[13]</cross-ref>. Forman F. et al. Vaccine Volume 30, Supplement 5 2012 F12 F23.
HPV type-specific distribution in 2855 cervical cancer cases (IARC studies)

% HPV type-specific infections among HPV + women
(singl eand multiple infections together)
HPV and Cancer

Cervical cancer: ≈ 99.7% contain HPV.
Vulvar cancer: ≈ 50% contain HPV.
Vaginal cancer: ≈ 65% contain HPV.
Penile cancer: ≈ 35% contain HPV.
Anal cancer: ≈ 95% contain HPV.
Orofaryngeal Cancer: ≈ 60% contain HPV.
HPV vaccines

• Profylactic.
• Recombinant L1 capsids (VLP).

<table>
<thead>
<tr>
<th>Gardasil.</th>
<th>Cervarix.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HPV-6, HPV-11, HPV-16, HPV-18.</td>
<td>- HPV-16, HPV-18.</td>
</tr>
<tr>
<td>- Yeast cells.</td>
<td>- Insect cells.</td>
</tr>
<tr>
<td>- Tre doses: 0, 2, 6 months.</td>
<td>- Tre doses: 0, 1, 6 months.</td>
</tr>
<tr>
<td>- Merck.</td>
<td>- GlaxoSmithKline Biol.</td>
</tr>
</tbody>
</table>
Ännu bättre cancervård
Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices

Emiko Petrosky, MD1,2, Joseph A. Bocchini Jr, MD3, Susan Hariri, PhD2, Harrell Chesson, PhD2, C. Robinette Curtis, MD4, Mona Saraiya, MD5, Elizabeth R. Unger, PhD, MD6, Lauri E. Markowitz, MD2 (Author affiliations at end of text)
Summary

• Sexually transmitted HPV infections are common.
• The majority of the HPV infections are cleared.
• In rare cases, high-risk HPVs persist.
• Persistent, high-risk HPV types may cause pre-malignant lesions (screening programs).
• High grade lesions may progress to cancer.
• 99.7% of cervical cancers contain HPV DNA.
• Two prophylactic vaccines: Gardasil & Cervarix
Human papillomavirus

Capsid: L1 + L2 proteins

$\varnothing=50\text{nm}$

Genome: 8kb, dsDNA
HPV-16 genome

Early genes

Late genes
Early mRNAs:
- E6
- E7

Late mRNAs:
- L2
- L1

Legend:
- p97
- p670
- LCR
- E1
- E2
- E3
- E4
- E5
- E6
- E7
- L1
- pAL

Start codons:
- AUG

Translated proteins:
- pAE

Annotation:
- LC5
- p97
- p670
Papillomavirus life cycle

1) Get into a cell.

2) Replicate the DNA genome.

3) Produce L1 and L2 proteins.

4) Form virions.
Papillomavirus life cycle is strongly linked to cell differentiation.
Many cellular factors may be involved in HPV entry!
HPV replication cycle

L1  L2

E1  E2

E6  E7
Papillomavirus life cycle is strongly linked to cell differentiation.
HPV genom

E1

E2
Papillomavirus life cycle is strongly linked to cell differentiation.
HPV-16 genome

Early genes

Late genes
1. Active cell division.
Papillomavirus life cycle is strongly linked to cell differentiation.
2. Stop apoptosis.
Low-risk & High-risk

• E6 och E7 and function.
Papillomavirus life cycle is strongly linked to cell differentiation.
HPV associated lesions in cervix.

NORMAL

LSIL

HSIL

TUMOR

(hnRNP A2/B2)
Normal epithelium

High-grade lesion
1) pRB - (cellcycle-Inactivation ofregulator).

2) Inactivation of p53 - (apoptosis-regulator).
Cancer

1) Inactivation of pRB - (cellcycle-regulator).

2) Inactivation of p53 - (apoptosis-regulator).

3) Signals of proliferation - (growth factors).

4) Activation of telomerase expression - (chromosome replication).

5) Inactivation of protein-phosphatase 2A (PP2A)
Summary

1. HPV lacks DNA polymerase.

2. HPV activates cell proliferation to gain access to cellular DNA polymerase (pRB & p53).

3. Persistent HPV infections allow time for cellular mutations.

4. Cellular mutations and HPV can together cause cancer.