The Natural History of HPV Infection
What’s happening brother?

Professor Marc Goodman
Disclosure Information

I have no financial relationships to disclose.

I will not discuss off label use and/or investigational use in my presentation.
Estimated New Cancer Cases and Cancer Deaths Worldwide for Leading Cancer Sites by Level of Economic Development

### Estimated New Cancer Cases

**Developed**
- Breast: 692,200
- Colon & rectum: 337,700
- Lung & bronchus: 241,700
- Corpus uteri: 142,200
- Stomach: 102,000
- Ovary: 100,300
- Non-Hodgkin lymphoma: 84,800
- Melanoma of the skin: 81,600
- Pancreas: 80,900
- Cervix Uteri: 76,500
- All sites but skin: 2,584,800

**Developing**
- Breast: 601,900
- Cervix uteri: 453,300
- Lung & bronchus: 272,000
- Stomach: 247,000
- Colon & rectum: 232,400
- Liver: 224,000
- Corpus uteri: 144,900
- Esophagus: 137,900
- Ovary: 125,200
- Leukemia: 93,400
- All sites but skin: 3,453,600

### Estimated Deaths

**Developed**
- Breast: 189,500
- Lung & bronchus: 188,400
- Colon & rectum: 153,900
- Pancreas: 79,100
- Stomach: 70,800
- Ovary: 64,500
- Liver: 39,900
- Leukemia: 38,700
- Non-Hodgkin lymphoma: 33,500
- Corpus uteri: 33,200
- All sites but skin: 1,223,200

**Developing**
- Breast: 260,000
- Cervix Uteri: 242,000
- Lung & bronchus: 239,000
- Stomach: 202,900
- Liver: 177,700
- Colon & rectum: 134,100
- Esophagus: 115,900
- Ovary: 75,700
- Leukemia: 75,100
- Brain, nervous system: 50,300
- All sites but skin: 2,122,600
Globally, HPV infection accounts for an annual 529,000 cervical cancer cases and 275,000 cervical cancer-associated deaths.

An estimated 86% of cervical cancer cases and 88% of related deaths occur in developing countries: single biggest cause of age-weighted years of life lost.
Age-Standardized Incidence Rates for Cervix Cancer

- Colombia 21.5
- Venezuela 31.4
- Guyana 44.7
- Ecuador 27.1
- Peru 34.5
- Bolivia 36.4
- Brazil 24.5
- Paraguay 35.0

- Dem Rep Congo 21.3
- Congo Rep 27.2
- Gabon 24.0
- Angola 30.0
- Zambia 52.8
- Zimbabwe 47.4
- Swaziland 50.0

- Mauritania 35.1
- Senegal 34.7
- Mali 37.7
- Gambia 32.4
- Sierra Leone 41.9
- Guinea 56.3
- Cote d’Ivoire 26.9
- Ghana 39.5
- Togo 30.0
- Benin 35.0
- Nigeria 33.0
- Cameroon 24.0

- Mongolia 28.4
- Kyrgyzstan 26.5

- India 27.0
- Nepal 32.4
- Bangladesh 29.8
- Myanmar 26.4
- Thailand 24.5
- Cambodia 27.4
- Laos 22.1
- PN Guinea 23.2

- Somalia 20.8
- Kenya 23.4
- Madagascar 27.2
- Uganda 47.5
- Tanzania 50.9
- Zambia 52.8
- Malawi 50.8
- Mozambique 50.6
- South Africa 26.6
- Lesotho 35.0

- Guatemala 30.5
- Honduras 37.8
- El Salvador 37.2
- Nicaragua 39.9
- Panama 25.3
- Jamaica 45.7
- Cuba 23.1
- Dom Rep 29.7

- Guinea 56.3
- Cote d’Ivoire 26.9
- Ghana 39.5
- Togo 30.0
- Benin 35.0
- Nigeria 33.0
- Cameroon 24.0

- < 7.0
- < 12.9
- < 20.2
- < 29.6
- < 56.3

Ubiquitous in humans:
- skin and mucosal lining
Mucosal HPVs are sexually transmitted
The most frequent STI
High detection in sexually active men and women
Not detected in virgins
Major Steps in the Development of Cervical Cancer

Schiffman et al. Lancet 2007
Natural History of Cervical Cancer
Infection, Persistence and Invasion

Sexual activity

Normal epithelium
HPV infection
CIN1
LSIL

CIN2
HSIL

CIN3/CIS

Invasive cancer

HPV INFECTION
PERSISTENT INFECTION
INVASION

Months
1-15 Years
Decades

80%
20%

CIN = Cervical Intraepithelial Neoplasia
SIL = Squamous Intraepithelial Lesion

Adapted from Xavier Castellsagué
Sexual encounter with HPV infected partner

Acquisition of HR HPV

Persistence of HR HPV infection

Pre-invasive cervical lesion

Invasive cervical cancer

Primary Prevention: HPV vaccination

Secondary Prevention: Screening

Cervical cytology

HPV DNA testing

Adapted from Tota et al, Prev Med 2011
HPV transmission dynamics are dependent on both viral and host factors, defined by susceptibility (e.g., HPV serostatus among women), contact rate per unit time, transmission probability, and duration of infectiousness.

Factors increasing $R_{01}$
- Greater number of partners (c)
- HIV (d, $S_{02}$)
- Herpes simplex virus 2 (d)
- Chlamydia trachomatis (d)
- Smoking* (d)
- HLA* (d)
- Increasing viral load* (p)

Factors decreasing $R_{01}$
- Condom use* (c)

Factors with unknown direction of effect on $R_{01}$
- Oral contraceptive use (d)
- HIV (p)
- Concurrent sexually transmitted infections (p)
- Male circumcision ($S_{02}$)

Factors increasing $R_{02}$
- Greater number of partners (c)
- HIV (d, $S_{01}$)
- Increasing viral load* (p)

Factors decreasing $R_{02}$
- Condom use* (c)
- Vaccination ($S_{02}$)

Factors with unknown direction of effect on $R_{02}$
- Male circumcision (d, p)
- Bacterial vaginosis ($S_{01}$)
- Oral contraceptive use ($S_{01}$)
- Vaginal practices ($S_{01}$)
- HIV (p)

$R = (R_{01} \times S_{01}) \times (R_{02} \times S_{02})$

$R_{01} = c \times d \times p$

$R_{02} = c \times d \times p$
70% of the participants had at least 1 anal HPV during the 1.3 yr follow-up period

Anal-cervical specimen pairs from 1,378 women at baseline

Anal-cervical specimen pairs from 431 participants with 2+ visits (1508 total visits)

Women with a cervical HPV infection had more than 3-fold increased risk of concurrent anal infection

70% of the participants had at least 1 anal HPV during the 1.3 yr follow-up period

Hernandez et al. CEBP 2005

Goodman et al, JID 2008
Anal-Cervical HPV Concordance

Relative Risk

Cervical → Anal

Anal → Cervical

Goodman et al, JID 2010
# Meta-Analysis of Genital HPV Concordance between 2,972 Heterosexual Couples

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>Total no. of couples with HPV-positive females</th>
<th>No. of couples with males with same HPV types*</th>
<th>Concordance (95% CI)</th>
<th>$i^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>16</td>
<td>605</td>
<td>173</td>
<td>0.361 (0.227-0.520)</td>
<td>86</td>
</tr>
<tr>
<td>Studies that recruited couples with male partners who had HPV-related disease</td>
<td>4</td>
<td>36</td>
<td>24</td>
<td>0.658 (0.485-0.797)</td>
<td>0</td>
</tr>
<tr>
<td>Studies without HPV-disease-based inclusion criteria for males</td>
<td>12</td>
<td></td>
<td></td>
<td>0.272 (0.150-0.442)</td>
<td>88</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total no. of couples with HPV-positive males</th>
<th>No. of couples with females with same HPV types*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>15</td>
</tr>
<tr>
<td>Studies that recruited couples with female partners who had HPV-related disease</td>
<td>10</td>
</tr>
<tr>
<td>Studies without HPV-disease-based inclusion criteria for females</td>
<td>5</td>
</tr>
</tbody>
</table>

**NOTE:** Concordance estimates are from random-effects meta-analysis. Analyses included all partners, regardless of HPV status, of HPV-positive individuals for whom studies reported appropriate concordance data.

*Both members of the couple infected with 1 or more of the same HPV types.

- **36% of men have the same HPV type as their partner**
- **55% of women have the same HPV type as their partner**
Primary Route of Genital HPV Infection

Sexual Intercourse

✓ HPV efficiently transmitted between sexual partners
✓ Rates of genital transmission from women to men may be higher than from men to women
  • Epithelial cells of the penile skin may be more resistant to HPV infection than the cervical epithelium
  • Duration of HPV infection may be shorter in men than in women
  • HPV testing may be less sensitive in men than in women
Chains of Affection
The Structure of Adolescent Romantic and Sexual Networks

Bearman et al, Am J Sociol, 2004
Sexual network features affecting the spread of HPV between partners

- Number of sexual links between the 2 partners to other members of the larger sexual network
- Concurrent sexual partners external to the couple
- Short gap lengths between previous sexual partners and the formation of the new sexual partnership
Prevalence of HPV in recently formed partnerships, by men's and women's histories with partners external to the dyad

The prevalence of HPV strongly associated with the history of sexual activities with other partners.
Prevalence of HPV in recently formed partnerships, by men's and women's lifetime number of vaginal sex partners

Burchell et al. JID 2014
## Incidence of Genital HPV Transmission among Heterosexual Couples

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Discordant Couples</th>
<th>Incidence per 100 person-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hernandez, EID 2008</td>
<td>United States</td>
<td>25</td>
<td>Male-to Female: 4.5 (1.5-9.3) Female-to-Male: 27.8 (19.0-38.3)</td>
</tr>
<tr>
<td>Burchell, JID 2011</td>
<td>Canada</td>
<td>179</td>
<td>Male-to Female: 3.5 (2.7-4.5) Female-to-Male: 4.0 (3.0-5.5)</td>
</tr>
<tr>
<td>Mbulawa, JID 2013</td>
<td>South Africa</td>
<td>486</td>
<td>Male-to Female: 1.2 (0.8-1.7) Female-to-Male: 2.8 (2.0-3.9)</td>
</tr>
<tr>
<td>Widdice, JID 2013</td>
<td>United States</td>
<td>25</td>
<td>Male-to Female: 9.2 (1.1-33.3) Female-to-Male: 21.4 (7.8-46.5)</td>
</tr>
<tr>
<td>Nyitray, JID 2014</td>
<td>United States</td>
<td>65</td>
<td>Male-to Female: 0.7 (1.1-33.3) Female-to-Male: 1.2 (0.7-2.0)</td>
</tr>
</tbody>
</table>
Incidence of Genital HPV Transmission among Heterosexual Couples

- Transmission from men to women was lower than the incidence from women to men, supporting the notion that men acquire more transient infections than women.
Incidence of Genital HPV Transmission among Heterosexual Couples

Per partnership transmission probability ~20% (95% CI: 16–24%)

Hernandez et al Emerg Infec Dis 2008
Incidence of Genital HPV Transmission among Heterosexual Couples

• 'Transmission' rates influenced by the interval between visits
• Detection of HPV DNA that is not an established infection may lead to overestimations of HPV transience and lead to higher transmission rate estimations when measured over short intervals
Type-specific genital transmission incidence of HPV in discordant heterosexual couples stratified by relationship duration

- ≤2 y—Men: 12-mo incidence proportion, 0.89 (0.76–1.00)
- ≤2 y—Women: 12-mo incidence proportion, 0.34 (0.05–0.63)
- >2 y—Men: 12-mo incidence proportion, 0.09 (0.01–0.17)
- >2 y—Women: 12-mo incidence proportion, 0.02 (0.00–0.05)
Rate of HPV Transmission Between Heterosexual Couples by Source and Target Site

<table>
<thead>
<tr>
<th>Source Site</th>
<th>Target Site</th>
<th>Incidence per 100 person-months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-to-Female</td>
<td>Penis</td>
<td>Hand</td>
</tr>
<tr>
<td></td>
<td>Scrotum</td>
<td>Anus</td>
</tr>
<tr>
<td>Female-to-Male</td>
<td>Anus</td>
<td>Scotum</td>
</tr>
<tr>
<td></td>
<td>Hands</td>
<td>Genital</td>
</tr>
<tr>
<td></td>
<td>Anus</td>
<td>Genital</td>
</tr>
<tr>
<td>Self-Inoculation</td>
<td>Male</td>
<td>Genital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anus</td>
</tr>
<tr>
<td>Female</td>
<td>Genital</td>
<td>Anus</td>
</tr>
<tr>
<td></td>
<td>Genital</td>
<td>Hand</td>
</tr>
</tbody>
</table>

Anus the only site of transmission on 4 of 78 transmission events

Male auto-inoculation was observed in 11 men, including 3 in which no heterosexual transmission was observed during the entire fu period.

Female autoinoculation all involved urine as a source and 3 targeted the hands.
Primary Route of Genital HPV Infection

Sexual Intercourse

✓ HPV efficiently transmitted between sexual partners
✓ Rates of genital transmission from women to men may be higher than from men to women
  • Penis shaft primary source of transmission to the cervix
  • Cervix and urine primary sources of infection to male genitals
  • Anus of women both a major source and target of heterosexual transmission

✓ Possible evidence for HPV transmission through non-penetrative sexual contact
Primary Route of **Genital** HPV Infection

Sexual Intercourse

However, other routes of infection are possible!

- Auto-inoculation between vagina and anus appears common
- Non-penetrative sex, including the use of fingers and sex toys, may increase the risk of anal transmission
**Prevalence of Oral HPV Infection in the United States, 2009-2010**

- Oral HPV infection is significantly less common than genital HPV infection.
- Infections are more common among men (10.1%) than among women (3.6%).

**Primary Route of Oral HPV Infection Sexual?**

Strong associations of oral HPV prevalence with lifetime, as well as recent number of vaginal or oral sexual partners.
Having many oral sexual partners is associated with increased prevalence of oral HPV

Kreimer et al, 2004  OR=12.8 for no. recent oral sex partners 2+ vs 0-1 in HIV-infected population
D'Souza et al, 2009  OR=5.2 for 11+ vs 0-1 lifetime oral sex partners
Pickard et al, 2012  OR=4.0 for 5+ vs 0-1 lifetime oral sex partners

However, prospective studies have been inconsistent regarding an association of oral sexual behaviors with the acquisition of oral HPV

Edelstein et al, 2012  HR=3.7 for recent frequency of performing oral sex 1+ times / week
Pickard et al, 2012  No significant association
Kreimer et al, 2013  No significant association
Oral-genital contact not the only route of transmission!

NHANES data show oral HPV prevalence of 3.5% in those who reported never performing oral sex (Gillison et al, 2012)
Primary Route of **Oral** HPV Infection Sexual?

✓ Oral-anal contact (rimming)

Higher number of oral sex or rimming partners were strong risk factors for prevalent oral HPV infection in HIV-negative subject, but these behaviors were highly correlated.
Primary Route of **Oral** HPV Infection Sexual?

✓ Oral-oral contact

Some studies have shown an association of open-mouthed kissing and prevalence of oral HPV infection

D’Souza et al, 2009  
OR=17.4 for 6+ vs 0-5 open-mouth kissing partners in past year

Pickard et al, 2012  
OR=4.0 for 5+ vs 0-4 lifetime open-mouth kissing partners

Edelstein et al, 2012  
No association

Beachler et al, 2012  
No association
Primary Route of Oral HPV Infection Sexual?

- Oral sex: Having many oral sex partners is associated with increased prevalence of oral HPV
- Oral-anal contact (rimming)
- Open-mouth kissing
- Autoinoculation
Primary Route of **Oral** HPV Infection Sexual?

**Autoinoculation**

The strong associations between incident oral HPV infection and infection with the same HPV type at other anatomic sites indicate that transmission may occur through autoinoculation.
HPV Transmission Cycle and Factors Influencing Transmission Dynamics

- Contact rate per unit time
- Duration of infection
- Transmission probability

\[ R_{01} = c \times d \times p \]

\[ R_{02} = c \times d \times p \]

\[ R = (R_{01} \times S_{01}) \times (R_{02} \times S_{02}) \]
HPV Transmission Cycle and Factors Influencing Transmission Dynamics

- **Transmission probability**
  - \( R_{01} = c \times d \times p \)

- **Duration of infection**

- **Contact rate per unit time**

- **Proportion of susceptible men**
  - \( S_{01} \)

- **Proportion of susceptible women**
  - \( S_{02} \)

- **HPV infections of the oral cavity resolve more rapidly than cervical infections**

- Oral-genital contact rate lower than genital-genital contact rate

- HPV transmission probability to oral cavity lower than to cervix

- **Factors for which the direction of association is unclear and suggested in this figure.**

- Veldhuijzen et al. Lancet Inf Dis 2010
Why is There a Lower Prevalence and Incidence of HPV Infection in the Oral Cavity Compared with Anogenital Sites?

- Lower viral load in the oral cavity resulting in reduced HPV detection
- Transmission of HPV to oral cavity more difficult than to anogenital sites because of differences in local mucosal immunity, permissiveness of cells to infection, epithelial resistance to microtrauma, salivary flow
- HPV clearance in oral cavity faster than anogenital sites
Summary

• HPV efficiently transmitted between sexual partners
• Rates of genital transmission from women to men may be higher than from men to women
• Possible evidence for HPV transmission through non-penetrative sexual contact
• Auto-inoculation between vagina and anus appears common
Acknowledgements

**CDC Cancer**
Mona Saraiya, Meg Watson, Zahava Berkowitz, Justin Miyamoto

**CDC HPV Lab**
Elizabeth Unger, Martin Steinau, Daisy Lee, Mariella Zamaroon, Julia Gargano

**Battelle**
Christopher Lyu, Dale Rhoda, April Greek

**Florida**
Youjie Huang, Jill Mackinnon, Carlos Alvarez

**Florida Central Lab**
Ed Wilkinson, Martha Campbell, Thompson Amy Wright

**Louisiana**
Ed Peters, Lauren Cole

**Michigan**
Glenn Copeland, Lara Ashley, Won Silva

**Iowa**
Charles Lynch, Freda Selk

**Los Angeles**
Maria Sibug-Saber, Wendy Cozen

**Hawaii**
Brenda Hernandez

**Kentucky**
Claudia Hopenhayn, Amy Christian, Tom Tucker HPV Typing of Cancers Workgroup Multiple Pathology Labs in 7 Cancer Registries
Early coordination between the health and education sectors is necessary to establish a feasible vaccination schedule for a multi-dose vaccine.

The value of intensive training must be balanced with the expense and time required for implementation and participation.

A range of approaches to community outreach, including mass media, trusted and influential individuals in the community, and the girls themselves play a key role in educating parents and each other about vaccination.

Simple language and pictures are best to convey key messages for diverse audiences.