Epidemiology and natural history of HPV cervical cancer: New opportunities for prevention

Anne F. Rositch, PhD, MSPH
Assistant Professor
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Sidney Kimmel Comprehensive Cancer Center
Cervical Cancer

Cervical cancer is the 4th most common cancer in women worldwide

528,000 new cases and 266,000 deaths globally (2012)
12,820 new cases and 4,210 deaths in the US (2017)

Estimated Cervical Cancer Incidence Worldwide in 2012

[Image of a world map showing different shades indicating the incidence rates of cervical cancer.]
Global age-specific incidence of cervical cancer

The Americas

ICO HPV Information Center; Rositch AF, et al. Cancer 2014; 120(13), 2032-2038
Hysterectomy-corrected ICC incidence

Age-standardized rate

Uncorrected: 11.7 per 100,000 (11.5, 11.8)
Corrected: 18.6 per 100,000 (18.3, 18.9)
ICC incidence by age and race

Rositch AF, et al., Cancer 2014;
Age-standardized mortality rates, 2002-2012

Percent difference: 78%

Annual Mortality per 100,000 women

Uncorrected

3.2  5.7

White  Black

© 2008, Johns Hopkins University. All rights reserved.
Age-standardized mortality rates

The black-white disparity increased 44% after correction.

Percent difference: 115%

Beavis and Rositch, Cancer 2017
Results: Trends in Mortality Rates

<table>
<thead>
<tr>
<th>Year</th>
<th>APC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected</td>
<td>2000-12</td>
</tr>
<tr>
<td>Corrected</td>
<td>2000-12</td>
</tr>
</tbody>
</table>

Annual mortality per 100,000 women

Age (Years)

black race

- Uncorrected
- Corrected
High risk HPV infection is necessary, but not sufficient for development of invasive cervical cancer

More than 100 genotypes identified which infect human epithelium, ~50 which specifically infect the anogenital tract

Approximately 14-18 are high risk (HR-HPV) or oncogenic.
  - HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82

Remaining HPV types are not associated with cancer (low risk or non-oncogenic), but can cause low grade cervical abnormalities or benign proliferative warts (esp HPV 6 and 11)
Incremental Contributions of HPV Types to cervical cancer

% of Cancers

© 2008, Johns Hopkins University. All rights reserved.
Working Model of Cervical Carcinogenesis

“Loss of detection”
Median duration: 8-11 months

- Normal cervix
- HPV infection
- Persistence
- High-grade Precancer (HSIL/ CIN2-3)
- Invasion

• Innate immunity
  • Antibody
  • Cytotoxic T-cell (CTL) response

• Immune suppression
  • HIV
  • renal transplant
• HLA
• viral type(?)
• viral load (?)
• viral variants (?)

• sexual behavior
• partner sex history

• Viral type
• Viral load (?)
• Viral variants
• Parity
• Smoking
• Inflammation
• Hormones/OC
Most HPV infections are “transient”
Natural History of HPV and Cervical Cancer

- Normal cervix
- HPV-infected cervix
- Viral persistence and progression
- Precancerous lesion
- Regression
- Invasion
- Cancer

HPV prevalence over time:
- 15 years
- 30 years
- 45 years

Schiffman & Castle, NEJM, 2005
Evolving Screening Guidelines

• Historical: annual screening with Pap smear and cytology

• 2003: American Cancer Society Guidelines begin recommending less than annual screening depending on type of test
  • Conventional cytology annual, LBC every 2 years; over 30 and 3 normal results every 2-3 years

• 2009: American Congress of Obstetricians & Gynecologists Guidelines recommend every 2-3 year screening
  • Pap every 2 years; over 30 and 3 normal results every 3 years; Co-testing every 3 years

• 2012: Guidelines from three major professional organizations: consensus on screening no more than every 3 years
  • Pap every 3 years; Co-testing every 5 years
# New draft screening guidelines

## Draft: Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women ages 21 to 65 years</td>
<td>The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women ages 21 to 29 years. The USPSTF recommends either screening every 3 years with cervical cytology alone or every 5 years with high-risk human papillomavirus (hrHPV) testing alone in women ages 30 to 65 years. See the Clinical Considerations section for the relative benefits and harms of alternative screening strategies for women age 30 years or older.</td>
<td>A</td>
</tr>
<tr>
<td>Women older than age 65 years</td>
<td>The USPSTF recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. See the Clinical Considerations section for a discussion of adequate prior screening and risk factors that support screening after age 65 years.</td>
<td>D</td>
</tr>
<tr>
<td>Women younger than age 21 years</td>
<td>The USPSTF recommends against screening for cervical cancer in women younger than age 21 years.</td>
<td>D</td>
</tr>
<tr>
<td>Women who have had a hysterectomy</td>
<td>The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.</td>
<td>D</td>
</tr>
</tbody>
</table>

Note: The first three recommendations apply to women who have a cervix, regardless of their sexual history or HPV vaccination status. None of these recommendations apply to women who have been diagnosed with a
Single cytology not very sensitive or reproducible

Cuzick et al., IJC, 2006
Mayrand et al., NEJM, 2007

Cytology Positivity

HART
Tuebingen
Hannover
Jena
French Public
French Private
Seattle
Canada

Combined
HPV DNA testing more reproducible and sensitive

Cuzick et al., IJC, 2006
Mayrand et al., NEJM, 2007

Graph showing HPV positivity rates for different locations:
- HART
- Tuebingen
- Hannover
- Jena
- French Public
- French Private
- Seattle
- Canada
- Combined

CIN 2+
High NPV allows safe increase in screening interval

Dillner et al., BMJ, 2008

0.95%
0.28%
0.22%
HPV genotyping

The cumulative incidence of CIN3 or greater over a 10-year period in women ages 30 and older as a function of a single HPV result at enrollment.
Ultimate goal – maintain sensitivity with substantial increase in specificity

Challenges—cost, clinical feasibility/translation, sample types and buffers, objective vs. subjective output
AHA! THE SURE SIGN OF PROMISCUITY!!
1st generation HPV vaccines

• **Gardasil®, Merck Research Laboratories (MRL)**
  - FDA approved June 2006
  - Targets HPV types 16 & 18 ~70% of cervical cancer and 6 & 11 ~90% of anogenital warts

• **Cervarix™, GlaxoSmithKline (GSK)**
  - FDA approved October 2009
  - Targets HPV types 16 & 18 ~70% of cervical cancer
  - Some cross-protection for HPV-31 and HPV-45

Both are safe – no risk of infection, adverse events minor--site injection pain, fainting

Neither impact pre-existing HPV16/18 (6/11) infection
  - Uncertain impact in women with prior exposure (seropositive) but not currently ‘infected’ (DNA negative)—new post-tx studies are promising
Nonavalent vaccine- current approval

In December, 2014 the FDA approved Gardasil 9

- Nonavalent HPV vaccine: types 6, 11, 16, 18, 31, 33, 45, 52, 58
- Estimated 90% reduction of cervical cancer and similar percentage of other HPV-associated cancers

<p>| TABLE 2. Summary of HPV Vaccine Clinical Trials Performed in Cervical Cancer Populations |
|-----------------------------------------------|-----------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Trial</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUTURE I/II</td>
<td>Women aged 15–26 y</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Gardasil (quadrivalent) (Merck)</td>
</tr>
<tr>
<td></td>
<td>N = 7864</td>
</tr>
<tr>
<td>Control</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N = 7865</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>4 y</td>
</tr>
<tr>
<td>Persistent Viral Infection Efficacy</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>(≥6 Months)</td>
<td>Disease Efficacy</td>
</tr>
<tr>
<td></td>
<td>CIN2+(98.2%)</td>
</tr>
<tr>
<td>PATRICIA</td>
<td>Women aged 15–25 y</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Cervarix (bivalent) (GlaxoSmithKline)</td>
</tr>
<tr>
<td></td>
<td>N = 7338</td>
</tr>
<tr>
<td>Control</td>
<td>Hepatitis A vaccine</td>
</tr>
<tr>
<td></td>
<td>N = 7305</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>4 y</td>
</tr>
<tr>
<td>Persistent Viral Infection Efficacy</td>
<td>91.4%-94.3%</td>
</tr>
<tr>
<td>(≥6 Months)</td>
<td>Disease Efficacy</td>
</tr>
<tr>
<td></td>
<td>CIN2+(92.9%)</td>
</tr>
<tr>
<td>CVT</td>
<td>Women aged 18–25 y</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Cervarix</td>
</tr>
<tr>
<td></td>
<td>N = 2643</td>
</tr>
<tr>
<td>Control</td>
<td>Hepatitis A vaccine</td>
</tr>
<tr>
<td></td>
<td>N = 2697</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>4 y</td>
</tr>
<tr>
<td>Persistent Viral Infection Efficacy</td>
<td>90.2%-93.1%</td>
</tr>
<tr>
<td>(≥6 Months)</td>
<td>Disease Efficacy</td>
</tr>
<tr>
<td></td>
<td>CIN2+(89.5%)</td>
</tr>
<tr>
<td>9-Valent Trial</td>
<td>Women aged 16–26 y</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Gardasil-9 (9-valent)</td>
</tr>
<tr>
<td></td>
<td>N = 5948</td>
</tr>
<tr>
<td>Control</td>
<td>Gardasil (quadrivalent)</td>
</tr>
<tr>
<td></td>
<td>N = 5943</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>4 y</td>
</tr>
<tr>
<td>Persistent Viral Infection Efficacy</td>
<td>Risk reduction: 96.0%¹</td>
</tr>
<tr>
<td>(≥6 Months)</td>
<td>Disease Efficacy</td>
</tr>
<tr>
<td></td>
<td>Risk reduction: 96.3%-96.7%¹</td>
</tr>
</tbody>
</table>

Abbreviations: CIN2+, cervical intraepithelial neoplasia, grade 2 or higher; CVT, Costa Rica HPV Vaccine Trial; HPV, human papillomavirus; PATRICIA, PA-pilloma TRIal against Cancer In young Adults.

Vaccine efficacy is summarized for the prevention of persistent infection and disease (CIN2+) for each study. Efficacy data shown are limited to participants who received all 3 scheduled doses and demonstrated no evidence of HPV exposure prior to vaccination.

¹For the 9-Valent Trial, risk reduction for disease or infection associated with HPV type-specific infections 31, 33, 45, 52, and 58 (types added to the 9-valent vaccine) is shown rather than absolute efficacy.⁴⁵⁻⁴⁷
2-dose vaccine recommendations

Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices

Weekly / December 16, 2016 / 65(49);1405–1408

Routine and catch-up age groups

- routine HPV vaccination at age 11 or 12 years but can start at age 9 years.
  - females through age 26
  - males through age 21 (aged 22 through 26 may be vaccinated)

Dosing schedules

- If initiating vaccination before their 15th birthday, the recommended immunization schedule is 2 doses of HPV vaccine
- Else 3 doses of HPV vaccine is recommended

*One dose trials are ongoing*
Natural History and prevention strategies

- Normal cervix
- HPV-infected cervix
- Clearance
- Viral persistence and progression
- Precancerous lesion
- Regression
- Invasion
- Cancer

15 years
30 years
45 years

Pap tests
HPV vaccination
HPV test 1
HPV test 2

Schiffman & Castle, NEJM, 2005
THANK YOU!

Feel free to contact me with questions: arositch@jhu.edu