The natural history and epidemiology of HPV and cervical cancer

Ellen Baker, MD, MPH
UT MD Anderson Cancer Center
Prevent Cancer Foundation Dialog for Action
June 17, 2020
Virtually

With thanks to:
Philip Castle, PhD, MPH – Albert Einstein College of Medicine, NYC, USA
Kathleen Schmeler, MD – UT MD Anderson Cancer Center, Houston, USA
No financial relationships to disclose
Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2014

*Per 100,000, age adjusted to the 2000 US standard population. 1 Uterus refers to uterine cervix and uterine corpus combined. 2 The mortality rate for liver cancer is increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, uterus, and colon and rectum are affected by these coding changes.

George Papanicolaou (1883-1962)

Pap smear
• Sample cells from cervix & place on a glass slide/vial
• Detect pre-cancerous and cancerous cells
• First reported in 1928 but not widely used until 1941
• Decreased cervical cancer rates by 70% in the US
Population Effects of Pap Screening

**Figure 2.** Cervical Cancer Mortality Rates in the United States and in the Netherlands, Age Standardized to the U.S. 2000 Population

Dr. Harald zur Hausen
Nobel Prize, 2008

Known Etiology of Cervical Cancer: Human Papillomavirus (HPV)

Primary Prevention:
• HPV Vaccination

Secondary Prevention:
• Screening with Pap test, HPV DNA test, VIA

Treatable Pre-Invasive Phase:
• Takes ~10 - 20y to progress from pre-invasive disease to cancer
• Ablation or Excision
Human papillomavirus (HPV)

Most common sexually transmitted disease
• Initial infection occurs as a teenager or young adult
• >80% of people will have HPV at some point in their life
• Global prevalence ~12%
  • 79 million Americans are currently infected
  • 14 million new infections/year in the US
• <5% will have significant pre-cancerous lesions
• <1% will develop invasive cervical cancer

https://www.cdc.gov/std/hpv/stdfact-hpv.htm
Human papillomavirus

- >100 HPV genotypes
- At least 14 HPV genotypes are considered high risk
- HPV types 16 and 18 cause
  - 70% Cervical cancers
  - >70% Anal cancers in men & women
  - 70% of Oropharynx cancers in men & women
  - 50% Penile cancers
  - 50% Vaginal and vulvar cancers
- HPV types 6 and 11 cause
  - 90% of genital warts
  - Recurrent Respiratory Papillomatosisis (RRP)
HPV–Associated Cancers in the US 2012-2016

About 44,000 new cases of HPV-associated cancers occurred in the US each year

12,015 cases of cervical cancer
19,000 oropharyngeal cancers (men and women)
~13,000 other cancers (vaginal, vulvar, penile, anus)

34,800 (79%) of these cancers can be directly attributed to HPV

About 32,100 of these cancers can be prevented with the 9-valent HPV vaccine

Average Number of New HPV-Associated Cancers by Sex in the U.S., 2012-2016

Females (24,886)
- Cervix: 48.6%
- Vagina: 16.2%
- Vulva: 14.0%
- Anus*: 17.6%
- Oropharynx: 11.9%
- Penis: 6.8%

Males (19,113)
- Cervix: 81.3%
- Vagina: 6.8%
- Vulva: 11.9%
- Anus*: 14.0%
- Oropharynx: 16.2%
- Penis: 17.6%
**HPV is necessary but not sufficient to develop cervical cancer**

Human papillomavirus infection

• Infects basal layers of cutaneous and mucosal squamous epithelium, primarily in transition zones (endo-ectocervical junction)
• E6 and E7 are viral oncoproteins expressed with persistent infection and viral replication

Interventions for prevention of cervical cancer

Schiffman and Castle, NEJM, 2005
Cervical Cancer Prevention Strategies

Cervical Cancer

US Incidence/Mortality
7.3/2.3 per 100,000

~290,000 women living with cervical cancer in the US

Texas Incidence/Mortality
9.1 (#6 in the US)
2.9 (#8 in the US)

Age-Adjusted Invasive Cancer Incidence Rates in Texas
Cervix Uteri, 2012 - 2016
By Health Service Region
Age-Adjusted to the 2000 U.S. Standard Population
Texas Rate: 9.2 / per 100,000

Age-Adjusted Cancer Mortality Rates in Texas
Cervix Uteri, 2012 - 2016
By Health Service Region
Age-Adjusted to the 2000 U.S. Standard Population
Texas Rate: 2.9 / per 100,000

https://gis.cdc.gov/Cancer/USCS/DataViz.html
https://www.dshs.texas.gov/tcr/data.shtm

www.cdc.gov/cancer/dataviz, June 2019
### Number of new cases of Cervical Cancer per 100,000 persons by race/ethnicity

- **All Races**: 7.3
- **White**: 7.2
- **Black**: 8.7
- **Asian / Pacific Islander**: 6.4
- **American Indian / Alaska Native**: 7.9
- **Hispanic**: 9.3
- **Non-Hispanic**: 7.0

13,170 new cases (2019)

---

SEER 21 2012-2016, Age-Adjusted
Number of deaths from Cervical Cancer per 100,000 persons by race/ethnicity

4,250 deaths (2019)

SEER 21 2012-2016, Age-Adjusted
Percent of New Cases by Age Group: Cervical Cancer

Cervical cancer is most frequently diagnosed among women aged 35-44.

Median Age At Diagnosis: 50
Median Age At Death: 58

SEER 21 2012-2016, All Races, Females

SEER 21 2012-2016, Age-Adjusted
Costs of prevention and treatment of HPV related disease in the US

- ~52,000,000 screening tests/year
- 2-3,000,000 women/year have abnormal tests
- Evaluation requires repeat visits, repeat testing
- ~350,000 women/year will have pre-cancerous lesions that require treatment and follow-up
- Cost of prevention and treatment of HPV related disease
  - ~$8 billion/year
    - $1 billion for cancer care
    - $6.6 billion for screening
    - $1.2 billion for follow up and treatment of abnormal results

Age Standardized Incidence of Cervical Cancer
Ranking of cervical cancer incidence in women 15-44 years (2018)
Recombinant L1 capsid proteins that form “virus-like” particles

Non-infectious and non-oncogenic

Antibodies prevent basement membrane binding

Produce higher levels of neutralizing antibody than natural infection

Vaccine not effective to treat an existing infection

Available vaccines:

Bivalent: Types 16, 18

Quadrivalent: Types 6, 11, 16, 18

Nonavalent: Types 6, 11, 16, 18, 31, 33, 45, 52, 58

Schiller J. Lowy D. Explanations for the high potency of HPV prophylactic vaccines Vaccine 35 (2018)4768-73
HPV Vaccine Recommendation

Preteens should finish HPV vaccine series by 13th birthday

Plus girls 13-26 years old who haven’t started or finished HPV vaccine series

Plus boys 13-26 years old who haven’t started or finished HPV vaccine series

https://www.cdc.gov/hpv/hcp/schedules-recommendations.html
Immunization of Boys

• Prevention of genital warts
• Potential prevention of oropharyngeal, anal, and penile cancer
• Decreased HPV transmission to female partners
• “Herd Immunity” - greater protection of the general public decreases infection in those who do not get vaccinated
## Dosage and scheduling

<table>
<thead>
<tr>
<th>Dose</th>
<th>Age range/ health condition</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 dose</td>
<td>• Boys and girls prior to 15&lt;sup&gt;th&lt;/sup&gt; birthday.</td>
<td>0, 6-12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If 1&lt;sup&gt;st&lt;/sup&gt; &amp; 2&lt;sup&gt;nd&lt;/sup&gt; dose administered &lt;5 months apart a 3&lt;sup&gt;rd&lt;/sup&gt; dose is required.</td>
</tr>
<tr>
<td>3 dose</td>
<td>• Boys and girls on or after 15&lt;sup&gt;th&lt;/sup&gt; birthday.</td>
<td>0, 1-2, 6 months</td>
</tr>
<tr>
<td></td>
<td>• Immunocompromised – HIV infection, cancer, autoimmune disease.</td>
<td></td>
</tr>
</tbody>
</table>

https://www.cdc.gov/hpv/hcp/schedules-recommendations.html
The HPV Vaccine is Safe

200 million doses of vaccine administered worldwide as of April 2014
HPV Vaccine Safety

Adverse Events:

• Injection site soreness
• Headache
• Fatigue
• Dizziness
• Fainting
• Nausea

Scheller et al., JAMA 2015
Vaccine Adverse Event Reporting System (VAERS)
Reduced risk of high grade dysplasia

Denmark: Risk of CIN 2/3 significantly reduced among vaccinated women (Baldur-Felskov)

Scotland: Risk of CIN 1/CIN2/CIN3 reduced by 29%, 50% and 55% in women 20-21 (Pollock)

USA: Estimated vaccine effectiveness for prevention of HPV 16/18 attributable CIN 2+ was 21%-72%, with greater reduction for vaccination >48 mos prior to screening (Hariri)

Australia: 73-93% reduction in genital warts (Garland)


Pollock, K., Kavanagh, K., Potts, A. et al. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. Br J Cancer 111, 1824–1830

Clinical Therapeutics/Volume 36, Number 1, 2014

HPV vaccine is cancer prevention.

Talk to the doctor about vaccinating your 11–12 year old sons and daughters against HPV.

#UCanStopHPV
<table>
<thead>
<tr>
<th>Cervical cancer screening recommendations, ACOG, ASCCP, USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG(^{17})</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Pap only</td>
</tr>
<tr>
<td>Pap-HPV cotest</td>
</tr>
<tr>
<td>High-risk HPV only</td>
</tr>
</tbody>
</table>

ACOG = American College of Obstetricians and Gynecologists; ASCCP = American Society for Colposcopy and Cervical Pathology; HPV = human papillomavirus; USPSTF = US Preventive Services Task Force
Why We Still Need Screening

• Poor vaccine uptake…but improving
• Existing vaccines do not cover all high-risk HPV types
• Vaccines do not treat pre-existing HPV infections

*Screening will be necessary for the foreseeable future and is still recommended after vaccination
Cervical cancer incidence in USA will decline more rapidly by increasing screening than by increasing HPV vaccination.
Sensitivity: CIN2+

- Cuzick et al., IJC, 2006
- Mayrand et al., NEJM, 2007
- Castle et al., LO, 2011
- Ferreccio et al., IJC, 2012

CIN2+

- HART
- Tuebingen
- Hannover
- Jena
- French Public
- French Private
- Seattle
- Canada
- Combined

Cytology/Pap

0% 10% 30% 50% 70% 90% 100%

HPV Testing

0% 70% 90% 100%
CIN3+ Risk Following a Negative Test

Dillner et al., BMJ, 2008
Reassurance Following a Negative Test in 1 Million Women Undergoing Routine Screening

Gage et al., JNCI, 2015
May 2018: WHO Director General’s call to action to eliminate cervical cancer as public health problem
The Architecture to Eliminate Cervical Cancer

**Vision:** To build a world without cervical cancer

**Threshold:** < 4 cases of cervical cancer per 100,000 woman-years

**2030 CONTROL TARGETS**

- **90%** of girls fully vaccinated with HPV vaccine by 15 years of age
- **70%** of women screened with an HPV test at 35 and 45 years of age
- **90%** of women identified with cervical disease receive treatment for precancerous lesions or invasive cancer

**SDG 2030:** Target 3.4 – 30% reduction in mortality from cervical cancer

*The 2030 targets and elimination threshold are subject to revision depending on the outcomes of the modeling and the WHO approval process*
Vaccinate your kids

....they grow up!
THANK YOU
BACK UP SLIDES
### Key Output 2: Increased coverage of screening & treatment for pre-cancer lesions

#### WHO recommendations
- Women aged 30-49 be screened at least once in their lifetime for cervical cancer, and rescreened every 5 years.
- HIV positive women should be screened every 3 years.
- Immediate treatment where possible.

#### Challenges
- *Expensive and complex screen and treat technologies complicate scaling-up*
- *New or optimized service delivery methods required for LMIC contexts*

#### Accelerators
- **Sufficient, affordable supply of screen and treat technologies & products**
  - Prompt certification of new products
  - Price reductions
- **National scale-up of screen & treat**
  - Simple algorithms need to be introduced for different settings
- **Increased quality and coverage of service delivery**
  - Countries detailed implementation plans to introduce and scale-up products and delivery models
  - Strengthen patient retention and linkage to treatment
Comparison of Cervical Cancer Screening Tests

<table>
<thead>
<tr>
<th></th>
<th>Pap smear (cytology)</th>
<th>VIA</th>
<th>HPV testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost</strong></td>
<td>Moderate ($10-$15/test)</td>
<td>Low (&lt;$5/test)</td>
<td>High, but lower in new formats (&lt;$10/test)</td>
</tr>
<tr>
<td><strong>Provider</strong></td>
<td>Cytotechnologist and cytopathologist</td>
<td>Nurses or mid-level providers</td>
<td>Lab technician</td>
</tr>
<tr>
<td><strong>Training/QA</strong></td>
<td>++ (Significant)</td>
<td>++ (Significant)</td>
<td>+ (Limited)</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>60-80%</td>
<td>50-80%</td>
<td>80-95%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>85-95%</td>
<td>70-80%</td>
<td>80-90%</td>
</tr>
<tr>
<td><strong>Min. # of visits</strong></td>
<td>2</td>
<td>1</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>Linking screening &amp; treatment</strong></td>
<td>Not possible in same visit</td>
<td>Immediate treatment possible</td>
<td>Possible in same visit or on same-day</td>
</tr>
<tr>
<td><strong>Home testing</strong></td>
<td>Not possible</td>
<td>Self sampling possible</td>
<td></td>
</tr>
<tr>
<td><strong>Inter-obs.variation</strong></td>
<td>++ (Significant)</td>
<td>+ (Minimal)</td>
<td></td>
</tr>
<tr>
<td><strong>Reproducibility</strong></td>
<td>Limited, unless using with digital imaging</td>
<td>Easily achievable</td>
<td></td>
</tr>
<tr>
<td><strong>Technology</strong></td>
<td>Open source/public domain</td>
<td>Proprietary</td>
<td></td>
</tr>
</tbody>
</table>

Sahasrabuddhe et al., Ca Prev Res (2012)

Slide Courtesy of V. Sahasrabuddhe.
Pap and Adenocarcinomas

Adegoke, J Women's Health 2012
Four Rounds of VIA: Success or Failure?

Cervical Cancer Incidence

Cervical Cancer Related-Death

Shastri et al., JNCI, 2014
HPV Testing Reduces the Risk of Cervical Cancer-Related Death in India

Sankaranarayanan et al., NEJM, 2009