A User-Friendly Guide To Cervical Cancer Prevention

Philip E. Castle, PhD, MPH
December 5, 2012
• I have received commercial HPV tests for research at a reduced or no cost from Roche, Qiagen, Norchip, and MTM.

• I am a paid consultant for BD and GE Healthcare; I have received a speaker’s honorarium from Roche.

• I am a paid consultant for Immunexpress on sepsis diagnostics.

• I am compensated as a member of a Merck Data and Safety Monitoring Board for HPV vaccines.
"I'll have an ounce of prevention."
1. Global Perspective of Cervical Cancer

2. Natural History of HPV: Rational Basis for Cervical Cancer Prevention

3. Targeting the Causal Factor: HPV Vaccines and Testing

4. New Screening Guidelines

5. Reaching the Hard-to-Reach
George Papanicolaou (1883-1962): Inventor of the Pap Smear
TIME TRENDS IN AGE-STANDARDIZED (WORLD) CERVICAL CANCER INCIDENCE IN FOUR NORDIC COUNTRIES

http://globocan.iarc.fr/
Estimated age-standardised incidence rate per 100,000
Cervix uteri, all ages
Today's Talk

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# Cervical Cancer Continuum: Old Model of Cervical Carcinogenesis

<table>
<thead>
<tr>
<th>Basal epithelium</th>
<th>Surface of epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>NORMAL</td>
</tr>
<tr>
<td>CONDYLOMATOUS ATYPIA</td>
<td>C.I.N. 1</td>
</tr>
<tr>
<td>VERY MILD DYSPLASIA</td>
<td>MILD DYSPLASIA</td>
</tr>
<tr>
<td>MILD DYSPLASIA</td>
<td>MODERATE DYSPLASIA</td>
</tr>
<tr>
<td>SEVERE DYSPLASIA</td>
<td>CARCINOMA IN SITU</td>
</tr>
<tr>
<td>INVASIVE CANCER</td>
<td></td>
</tr>
</tbody>
</table>
New Model of Cervical Carcinogenesis

Transient infection

Normal cervix  INFECTION  HPV-infected cervix  PROGRESSION  INVASION  Cancer

Persistent HPV

HPV-infected cervix  CLEARANCE  Precancer  REGRESSION?
Etiologic Contribution of HPV Genotypes

![Bar chart showing the fraction of cancers contributed by different HPV genotypes](chart.png)
Regional Variation of HPV Genotypes in CxCa

de Sanjose et al., Lancet Oncol, 2010
Natural History Profile of Prevalent HPV

% Clearance (100%-%Persistence)

Months

0 6 12 18 24 30 36 42 48 54 60 66 72 78 84

Progressed
Persisted
Cleared

Schiffman et al., Lancet, 2007
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Impact of Age on Vaccine Efficacy

Kjaer, Cancer Prev Res, 2009

Herrero et al., Cancer Discov, 2012
HPV-16/18 Clearance by Trial Arm

Baseline HPV16/18 Status

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Placebo (Hep A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Month HPV16</td>
<td>0%</td>
</tr>
<tr>
<td>12-Month HPV16</td>
<td>20%</td>
</tr>
<tr>
<td>6-Month HPV18</td>
<td>40%</td>
</tr>
<tr>
<td>12-Month HPV18</td>
<td>60%</td>
</tr>
<tr>
<td>6-Month HPV16&amp;18</td>
<td>60%</td>
</tr>
<tr>
<td>12-Month HPV16&amp;18</td>
<td>60%</td>
</tr>
<tr>
<td>6-Month HPV16&amp;18 (all doses)</td>
<td>60%</td>
</tr>
</tbody>
</table>

Hildesheim et al., JAMA, 2007
Sensitivity: CIN2+

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

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

Cytology/Pap

HPV Testing
%Cytology and HPV Positive: No CIN

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

HART
Tuebingen
Hannover
Jena
French Public
French Private
Seattle
Canada
Combined

Cytology Positivity

No CIN

0% 10% 30%

HPV Positivity

No CIN

0% 10% 30%
CIN3+ Risk Following a Negative Screening Test

Cumulative incidence of CIN3+ (per 10,000)

Time since initial testing (mos.)

Dillner et al., BMJ, 2008
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## Benefits vs. Harms

<table>
<thead>
<tr>
<th>Actual</th>
<th>Benefits</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>✡ Cervical cancer prevention</td>
<td>➢ Anxiety associated with a positive screening test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Potential stigmatization from the diagnosis of a sexually transmitted infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Discomfort from additional diagnostic and treatment procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Bleeding from treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Increased risk of pregnancy complications such as preterm delivery due to treatment.</td>
</tr>
</tbody>
</table>

| Surrogate | Early detection of CIN3 | Number of colposcopic referrals |
Harmonizing Management According To Risk

Castle et al., JLGTD, 2008
<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Recommended Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;21</td>
<td>No Screening!!!!</td>
</tr>
<tr>
<td>21-29</td>
<td>Cytology (3 Year)</td>
</tr>
<tr>
<td>30-64</td>
<td>HPV and Cytology Cotesting (5 Year) (Preferred) Cytology (3 Year) Acceptable)</td>
</tr>
<tr>
<td>65 and Older</td>
<td>No Screening with a 10-Year Negative Screening History</td>
</tr>
</tbody>
</table>

Saslow et al., CA Cancer J Clin, 2012
Cervical Cancer Incidence by Age (USA)

Castle and Carreon, JLGTD, 2010
Cytology Screening Interval: Cancer Risk vs. Colposcopy

<table>
<thead>
<tr>
<th>Lifetime (per 1,000)</th>
<th>Cancer Risk</th>
<th>Number of Colposcopies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every Year</td>
<td>3</td>
<td>2000</td>
</tr>
<tr>
<td>Every 2 Years</td>
<td>4 to 6</td>
<td>1080</td>
</tr>
<tr>
<td>Every 3 Years</td>
<td>5 to 8</td>
<td>760</td>
</tr>
</tbody>
</table>

Saslow et al., CA Cancer J Clin, 2012
Real World Performance

Katki et al., Lancet Oncol, 2011

Cumulative Incidence of CIN3+

Years Since Enrollment

3-yr risk for Pap- = 0.17%
5-yr risk for HPV- = 0.17%
5-yr risk for HPV-/Pap- = 0.16%
Algorithm for Cotesting in Women 30-64 Y.O.

Current Screening Guidelines

HPV+Pap Cotesting Every 5 Years*
Guideline Failures

Yabroff et al., AIM, 2009

Composite Measure (all 4 vignettes)

18-year old, non-sexually experienced, first visit

18-year old, sexually experienced 3 years before first visit

35-year old, hysterectomy for benign cause with 3 normal Pap tests

66-year old, non-resectable lung cancer with 3 normal Pap tests

Percentage With Guideline-Consistent Recommendations

- Obstetrics & Gynecology
- Internal Medicine
- Family Practice/General Practice

Yabroff et al., AIM, 2009
When Would Next HPV Test?  
35 years, Pap Normal and HPV Negative?

Saraiya et al., Arch Intern Med, 2009
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Cervical Cancer Mortality Map for The U.S.

## Cervical Cancer in Maryland

### TABLE 3.6

<table>
<thead>
<tr>
<th>RACE/ETHNIC GROUP</th>
<th>INCIDENCE</th>
<th>MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American/Black</td>
<td>20.0</td>
<td>7.1</td>
</tr>
<tr>
<td>White</td>
<td>23.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>19.8</td>
<td>N/A</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>10.6</td>
<td>N/A</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Rates are per 100,000 and are age-adjusted to the 2000 US standard population.

N/A means rates were suppressed if counts were fewer than 16 or if the population of the specific category (race, ethnicity) is less than 50,000.

US Incidence: ~8 per 100,000
Self Collection and HPV Testing in China

Zhao … Castle, JNCI, 2012
Screening in the Mississippi Delta

Castle et al., Prev Med, 2011
Final Comments

• HPV is the necessary but infrequent cause of cervical cancer.

• HPV vaccines and tests can be highly effective if used in an age-appropriate manner. HPV vaccines will prevent cancer and clinically important disease from occurring in the future. Screening prevents cancer now.

• Current screening guidelines are based on two basic principles:
  - Benefits to the few at-risk women must outweigh the harms to the generally healthy population.
  - Equal Risk = Equal Care
Final Comments

- It is impractical and very costly, and potentially very harmful, to screen women excessively in an attempt to prevent ALL cervical cancer.

- The greatest gains in cancer prevention will achieved by reaching those not currently getting services.