Hot Topic
The Future of Cervical Cancer Screening

Cervical Cancer Screening
Prabodh Gupta MD, FIAC
Incidence of Cervical Cancer Worldwide Data

International Association of Cancer Registries, GLOBOCAN 2002 and NCI: Division of Cancer Epidemiology and Genetics; dceg.cancer.gov/disparities/cervical

Rates per 100,000 woman-years, age-adjusted
Invasive Cervical Cancer

United States: Minor Problem

• 11th most common cancer in women
• 3rd most common gynecologic malignancy
• 12th leading cause of cancer deaths in women
  – 2nd leading cause in women 20-39 yrs
• Rate of 9.9 cases/100,000 and 3.1 deaths/100,000 annually
• 2007 estimated 11,150 new cases and 3,670 new deaths (~10 deaths/day)

Worldwide: Major Problem

• 2nd most common cancer among women, disproportionately affecting underserved populations
  – 80% developing countries
  – Highest rates Latin America, Caribbean, sub-Saharan Africa, South and SE Asia
• 1st most common gynecologic malignancy
• 3rd cause of cancer deaths in women
• ~789 deaths/day
Annual Age-adjusted Cancer Death Rates* Among Females for Selected Cancers, United States, 1930 to 2004

HPV Testing - Diagnostic Accuracy

(Koliopoulos G et al. Gyncol Oncol. 2007)

• Meta-analysis (25 studies)
  – HC2/PCR more sensitive than Cytology for HSIL, but, significantly less specific than Cytology
  – Combination of Cytology and HC2 highest sensitivity and lowest specificity

Conclusion:
– Reduction in mortality by HPV testing compared to Cytology is not established
Cross-Sectional Multiple Techniques Comparative Trail
(Belinson J et al. Gyncol. Oncol. 2001)

Shanxi Province, China. 1,997 women, \( \geq \) CIN II

Conclusion: HPV HC-II NOT READY for PRIME TIME
Accuracy of CIN Detection using ThinPrep Imager

(Davey E et. al. BMJ 2008).

- 55,164 split samples, Conventional / ThinPrep read by Imager

- **Imager read slides:**
  - Less unsatisfactory 1.8% vs. 3.1%, (p<0.001)
  - More abnormals 7.4% vs. 6.0%
  - More CIN I + lesions 2.8% vs. 2.2%
  - More biopsies proven CIN lesions

- Imager detected 1.29 more abnormal cases/1,000 specimens

**Conclusion: Improved sensitivity with Location guided screening**
Summary and Conclusions

- Pap smear is NOT SCREENING Test
- Good sampling and morphology are critical for accurate diagnosis
- HPV testing valuable for “atypicals” which are more common in liquid-based slides.
- Paradigm shift and economics challenges

- Anything is better than a lousy Pap Smear; Nothing better than a GOOD PAP SMEAR

Why change?
Because Cytology Misses CIN

- **Sampling**
  - Cells aren’t there

- **Locating**
  - Cells are there but are hard to find

- **Interpreting**
  - Cells are found but we are wrong
  - Even if we are right, *we don’t agree*
IMPACT OF THE VARIATIONS IN LESION PREVALENCE ON PPV AND NPV FOR CYTOLOGY

PPV: Positive predictive value
NPV: Negative predictive value
<table>
<thead>
<tr>
<th>Population</th>
<th>Endpoint</th>
<th>Subjects With an Endpoint</th>
<th>Quad HPV Vaccine</th>
<th>Placebo</th>
<th>% Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generally HPV Naïve</td>
<td>ASC-US (HC+)</td>
<td>213</td>
<td>289</td>
<td></td>
<td>26 (12, 39)</td>
</tr>
<tr>
<td></td>
<td>ASC-H</td>
<td>48</td>
<td>75</td>
<td></td>
<td>36 (6, 56)</td>
</tr>
<tr>
<td></td>
<td>LSIL</td>
<td>704</td>
<td>833</td>
<td></td>
<td>16 (7, 24)</td>
</tr>
<tr>
<td></td>
<td>HSIL</td>
<td>18</td>
<td>35</td>
<td></td>
<td>48 (6, 72)</td>
</tr>
<tr>
<td></td>
<td>Colposcopy/Biopsy</td>
<td>500</td>
<td>636</td>
<td></td>
<td>22 (12, 30)</td>
</tr>
<tr>
<td></td>
<td>Definitive Therapy</td>
<td>82</td>
<td>138</td>
<td></td>
<td>40 (21, 55)</td>
</tr>
</tbody>
</table>
“Conventional Pap smear screening, based on the few studies that avoided severe biases, showed specificity of 98%... and sensitivity of 51%....much lower than generally believed”

JOINT EFFECTS OF CHANGES IN SENSITIVITY, SPECIFICITY, AND LESION PREVALENCE ON THE POSITIVE PREDICTIVE VALUE OF A SCREENING TEST

*Specificity: dashed grey line: 95%; solid red line: 85%; dotted white line: 75%
It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change.

Charles Darwin

If you want to make enemies, try to change something.

Woodrow Wilson
Two Distinct Commercial HPV L1 VLP Vaccines

GlaxoSmithKline: Cervarix

- HPV16
- HPV18
- ASO4 Adjuvant (Aluminum + MPL)
- Made in insect cells

Merck: Gardasil

- HPV16
- HPV18
- HPV6
- HPV11
- Aluminum Adjuvant
- Made in yeast

Three intramuscular injections given over 6 months
**Merck vaccine: prophylactic efficacy results against HPV types in the vaccine (2006)**

<table>
<thead>
<tr>
<th>HPV Type/Condition</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Efficacy</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>*HPV16 or 18 CIN 2/3 or AIS</td>
<td>8487</td>
<td>0</td>
<td>8460</td>
<td>53</td>
</tr>
<tr>
<td>**HPV16 or 18 VIN2/3 or VaIN2/3</td>
<td>8641</td>
<td>0</td>
<td>8667</td>
<td>24</td>
</tr>
<tr>
<td>*HPV6, 11, 16, 18 Genital warts</td>
<td>7897</td>
<td>1</td>
<td>7899</td>
<td>91</td>
</tr>
</tbody>
</table>

Results in HPV DNA and seronegatives at baseline after three doses (*) or after at least one dose (**), as reported in Gardasil package insert.

Average Duration of Follow-up: 1.5 Years After the Last Vaccination

**Note: Protection against infection by other HPV types is limited.**
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70% of Cervical Ca
90% of Genital Warts
HPV Vaccines – Implications for Countries with Established Cervical Cancer Screening Programs

• Current recommendations for screening not changed – only 70% of cervical cancer covered by vaccines

• Further reduction of cervical cancer requires widespread acceptance of HPV vaccines and continued participation in effective screening (100% effective vaccine would reduce lifetime risks of cervical cancer by 66% compared with current screening programs*)

HPV Vaccines – Implications for Countries with Established Cervical Cancer Screening Programs

• Implications of widespread use of HPV vaccines will change the outcome of current screening programs
• Removal of HPV 16/18 from the population will substantially reduce the likelihood of significant precancerous disease (CIN2+)
## Expected Impact of HPV16-18 Vaccine Alone on the Incidence of Abnormal PAP

<table>
<thead>
<tr>
<th>PAP Categories</th>
<th>Mean Incidence %</th>
<th>HR HPV %</th>
<th>HPV16-18 %</th>
<th>Impact HPV16-18 Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>94</td>
<td>10</td>
<td>2.5</td>
<td>+</td>
</tr>
<tr>
<td>ASC-US</td>
<td>3</td>
<td>50 ~20</td>
<td>~25</td>
<td>++</td>
</tr>
<tr>
<td>LSIL</td>
<td>2.5</td>
<td>83</td>
<td>~25</td>
<td>+++</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.001</td>
<td>100</td>
<td>70</td>
<td>++++</td>
</tr>
</tbody>
</table>

### Total Reduction Abnormal PAP: ~15-20%

HPV Vaccines – Implications for Countries with Established Cervical Cancer Screening Programs

- Pap test only 50-70% sensitivity; 96% specificity
- HPV vaccines will prevent development of CIN2+ lesions and cancer by ≈50%; hence, positive predictive value for the Pap test is further reduced
- HR HPV (HCII) is 95% sensitive and 94% specific, although decreased in a vaccinated population
HPV Vaccines – Implications

• Harvard School of Public Health recently developed a cost-effective model for cervical cancer screening in a mixed vaccinated population; their conclusion:
  – Screening starting at 21-25 with Pap test/ASC-US HPV reflex
  – At age 30, HPV DNA screening; if positive, follow by Pap test; if both negative, reduced frequency of screening

• Development of more sensitive and specific screening tests are in the pipeline, including biomarkers focused on transformational events, such as E6/E7 gene product
Clinical medicine is a constantly changing arena to which we must adapt for ultimate patient benefit – HPV vaccines represent a paradigm shift and will impact both cervical neoplasia and efforts to screen for it.